RESEARCH IN NF COMPOUNDS

A FINAL REPORT

TO

THE OFFICE OF NAVAL RESEARCH

CONTRACT N00014-69-C-0015

NOVEMBER, 1970

A DIVISION OF AEROJET-GENERAL CORP.

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RESEARCH IN NF COMPOUNDS

A Report on Work Sponsored By

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ENVIROGENICS COMPANY
a division of
AEROJET-GENERAL CORPORATION
9200 East Flair Drive
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ABSTRACT

Alkylation reactions of difluoramine and direct fluorination reactions are reviewed. The following phases of earlier work were completed and the work was assembled in the form of manuscripts:

Mannich Reactions of 2-Fluoro-2,2-dinitroethanol;

Synthesis of N-Fluoronitramines;

Synthesis of Tris(carboalkoxyamino)methane;

N-Carbethoxyiminocarboxylic Acid Esters.

CONTRACT FULFILLMENT STATEMENT

This final report is submitted in fulfillment of the contract to the Office of Naval Research . This report covers the period 1 June 1970 to 30 November 1970.

Aerojet-General Corporation

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Project Manager

Approved:

W P Knight

W. P. Knight, Manager
Special Projects
Envirogenics Company

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INTRODUCTION

This is the final report under Contract N00014-69-C-0015, which was initiated on 1 December 1968. The following reports have been issued on this contract: Aerojet-General Reports No. 5015-01-1, May 1969 (Confidential); No. 5015-2, January 1967 (Unclassified); and No. 5015-3, July 1970 (Unclassified). This program is a continuation of earlier technical efforts under Contract Nonr 2655(00), summarized in Aerojet-General Report No. 3672, December 1968 (Confidential).

As part of the present program, some earlier work was refined to meet present journal requirements, and manuscripts were prepared for publication. The following manuscripts were prepared under the earlier contract and were published under the current one:

"Reactions of Carbonyl Compounds with Difluoramine," K. Baum, J. Amer. Chem. Soc., 90, 7083 (1968).

"Reaction of Acetylenes with Difluoramine," K. Baum, J. Amer. Chem. Soc., 90, 7089 (1968).

"Reactions of Aryldiazonium Fluoborates with Isopropyl Fluorocarbamate and with Difluoramine," K. Baum, J. Org. Chem., 33, 4333 (1968).

"Synthesis and Reactions of Alkyl Fluorocarbamates and Difluorocarbamates," V. Grakauskas and K. Baum, J. Amer. Chem. Soc., 91, 1679 (1969).

"Reactions of Chloro Olefins with Difluoramine," K. Baum, J. Org. Chem., 34, 2046 (1969).

"Reactions of Nitro and Nitroso Compounds with Difluoramine," K. Baum, J. Org. Chem., 34, 2049 (1969).

Direct Fluorination of Substituted Carbamates," V. Grakauskas and K. Baum, J. Org. Chem., 34, 2840 (1969).

"Some Reactions of Difluoramino Compounds with Bases and Reducing Agents," K. Baum, J. Org. Chem., 34, 3377 (1969).

The following manuscripts were prepared and published under the current contract:

"Substituent Constants of Difluoraminoalkyl and gem-Bis(difluoramino)-alkyl Groups," K. Baum, J. Org. Chem., 35, 1203 (1970).

"Direct Fluorination of Secondary Nitronate Salts," K. Baum, J. Org. Chem., 35, 846 (1970).

"Michael Reactions of 2-Fluoro-2,2-dinitroethanol and 2,2-Dinitropropanol with Olefinic and Acetylenic Acceptors," V. Grakauskas and K. Baum, J. Org. Chem., 34, 3927 (1969).

"Direct Fluorination of Ureas," V. Grakauskas and K. Baum, J. Amer. Chem. Soc., 92, 2096 (1970).

"Direct Fluorination of Amides," V. Grakauskas and K. Baum, J. Org. Chem., 35, 1545 (1970).

"Synthesis of α,α-Dinitro-N'-fluorodiimide N-Oxides," K. Baum, J. Org. Chem., 35, 2844 (1970).

"Alkylation Reactions of 2-Fluoro-2,2-dinitroethanol," V. Grakauskas, J. Org. Chem., 35, 3030 (1970).

"Reaction of Carbonyl Groups with Perchloric Acid, gem-Diperchlorates," J. Amer. Chem. Soc., 92, 2927 (1970).

The present report includes the manuscripts of two review articles which will be published in Intra-Science Chemistry Reports: "Alkylation Reactions of Difluoramine," K. Baum, and "Direct Liquid Phase Fluorination of Organic Compounds," V. Grakauskas.

The following manuscripts are included that have not yet been submitted for publication:

"Mannich Reactions of 2-Fluoro-2,2-dinitroethanol," V. Grakauskas and K. Baum.

"Synthesis of N-Fluoronitramines," V. Grakauskas and K. Baum.

"Synthesis of Tris(carboalkoxyamino)methane and N-Carbethoxyimino-carboxylic Acid Esters," V. Grakauskas.

The research described in the Mannich reaction paper was carried out in part under Contracts N60921-67-C-0290 and F08635-69-C-0125 with the Air Force Armament Laboratory and the Naval Ordnance Laboratory.

ALKYLATION REACTIONS OF DIFLUORAMINE

by

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I. INTRODUCTION

Nitrogen trifluoride has low basicity because of the electron-withdrawing effect of the three fluorines.[1] Salts of fluoramine with strong acids, on the other hand, are formed readily and are stable.[2] Difluoramine, as one would expect, possesses basicity intermediate

to that of nitrogen trifluoride and that of fluoramine. Thus, difluoramine is moderately soluble in strong acids, but there has been no conclusive evidence for salt formation. These properties are the basis of the chemistry of difluoramine in strongly acidic media such as concentrated sulfuric acid or fluosulfonic acid.

Difluoramine is alkylated by a variety of carbonium ions in these solvents. The reactions are of preparative significance as sources of organic difluoramino compounds and of theoretical interest as carbonium ion traps. Most nucleophilic reagents are protonated in the strong acids, and cation-cation repulsion negates their utility as carbonium ion traps. Reactions of difluoramine with various types of alkylating agents will be discussed.

II. DIFLUORAMINE PREPARATION

Difluoramine was first identified conclusively by Kennedy and Colburn[3] in 1959 as a byproduct of the reaction of arsenic with nitrogen trifluoride. Arsine and tetrafluorohydrazine were shown to be intermediates. Subsequently, other active hydrogen compounds were investigated as reducing agents for tetrafluorohydrazine, and a practical laboratory synthesis of difluoramine was developed using thiophenol.[4] In our laboratories, the acid hydrolysis of aqueous N,N-difluorourea, the fluorination product of urea,[5] was found to be a convenient direct method using conventional glassware. Another convenient method for the small scale synthesis of difluoramine is the hydrolysis of the commercially available trityldifluoramine.[6] Difluoramine is a sensitive explosive and adequate shielding must always be used.

III. OLEFINS AND SIMPLE CARBONIUM IONS AS ALKYLATING AGENTS

The first examples of the alkylation of difluoramine by carbonium ions were reported by Graham and Freeman.[7] In the presence of 96% sulfuric acid or BF_3-H_3PO_4 1, 1-dialkyl olefins gave the corresponding t-alkyldifluoramines. Trityl bromide reacted with difluoramine in SO_2 to give trityl difluoramine, and orthoesters reacted with monoesters to give products in which one alkoxygroup is replaced by difluoramine.

$$(CH_3)_2C = CH_2 \xrightarrow[H^+]{HNF_2} (CH_3)_3C\,NF_2$$

$$CH(OCH_3)_3 \xrightarrow{HNF_2} CH(OCH_3)_2NF_2$$

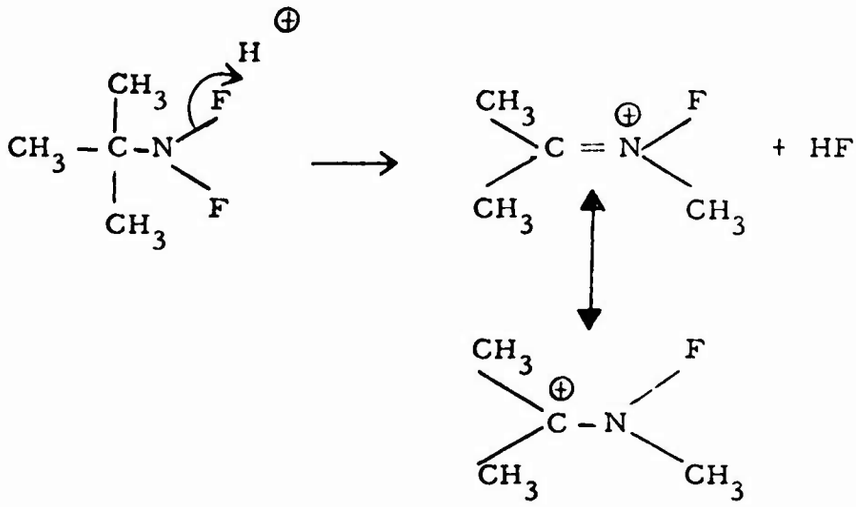
In the analogous reaction of difluoramine with cyclic olefins,[8] BF_3-H_3PO_4 was found to be a convenient catalyst because rearrangement of the product was minimized.

IV. REARRANGEMENT OF ALKYLDIFLUORAMINES

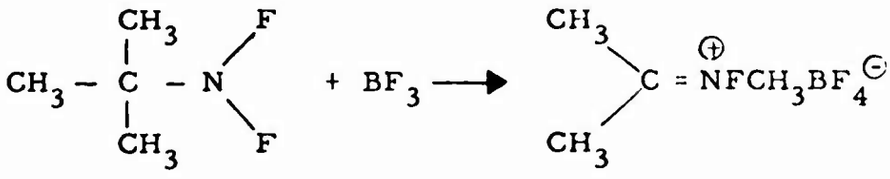
The reaction of triphenylmethyldifluoramine with concentrated sulfuric acid has been reported by Graham and Parker[9] to give difluoramine and triphenylmethyl cation. Thus, the difluoramine entity functions as a leaving group under the driving force of the formation of the highly stable trityl cation.

$$(C_6H_5)_2CNF_2 \xrightarrow{H_2SO_4} (C_6H_5)_3C^{\oplus} + HNF_2$$

Simple alkyldifluoramines were also found to react readily with concentrated sulfuric acid, but C-N cleavage was not observed.[10] Thus, t-butyldifluoramine reacted at 0° to give a homogeneous solution, shown by nmr spectra to contain HF and an ionic species identified as the N-fluoro-N-methylisopropylidenimonium ion. The methyl groups of this ion were nonequivalent, indicating positive charge on the nitrogen. The rearrangement is rationalized as a nucleophilic alkyl migration with fluoride leaving.



This rearrangement was also effected by a Lewis acid; boron trifluoride in pentane at -78°, gave the pure salt, N-fluoro-N-methyisopropylidenimonium fluoroborate.



Ethyldifluoramine also reacted with concentrated sulfuric acid, and acetonitrile was identified as the primary product by nmr. Acetonitrile was hydrated slowly under the reaction conditions to give acetamide.

$$CH_3CH_2NF_2 \xrightarrow{-HF} CH_3CN \longrightarrow CH_3CONH_2$$

The reaction of 1-difluoraminobutane with sulfuric acid did not follow the same course as that of ethyldifluoramine. The nmr spectra of the solution formed by shaking 1-difluoraminobutane with sulfuric acid were consistent with the propyl migration product, N-fluoro-N-propylmethylenimonium ion. The terminal methylenes, for example, were nonequivalent with normal cis and trans coupling constants to the fluorine.

$$CH_3CH_2CH_2CH_2NF_2 \longrightarrow \begin{matrix} H \\ \diagdown \\ C = \overset{\oplus}{N} \\ \diagup \\ H \end{matrix} \begin{matrix} F \\ \diagup \\ \\ \diagdown \\ CH_2CH_2CH_3 \end{matrix}$$

The rearrangement of 2-difluoraminobutane with sulfuric acid could be envisioned as taking place by methyl migration to give N-fluoro-N-methylpropylidenimonium ion

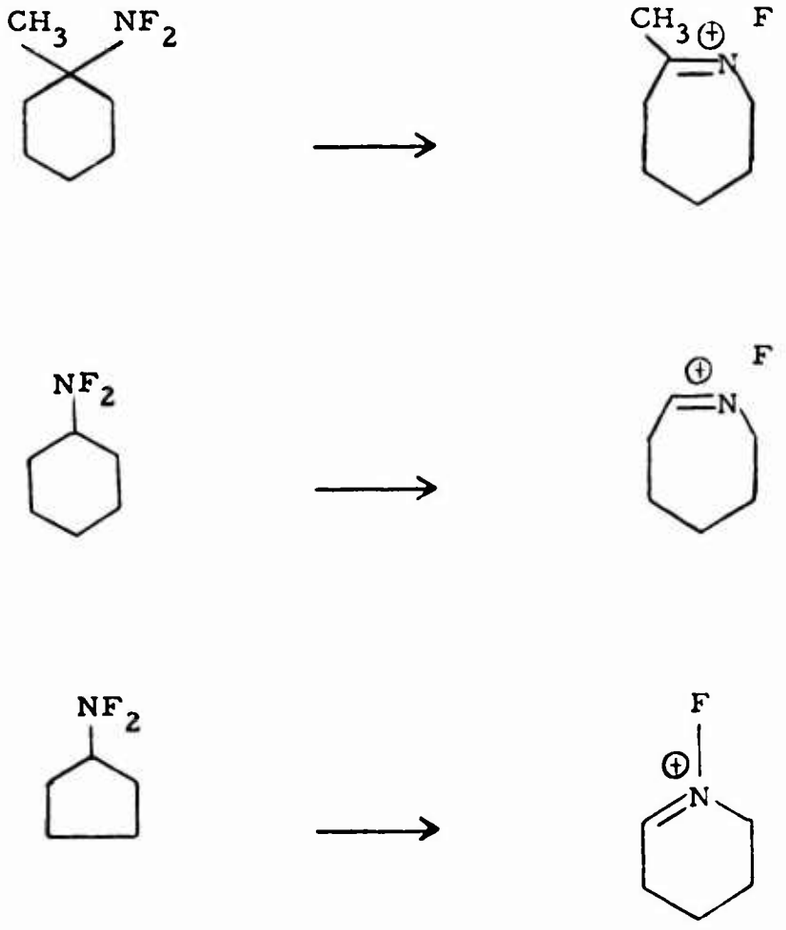
$$CH_3CHNF_2CH_2CH_2 \longrightarrow CH_3\overset{\oplus}{N}F \simeq CHCH_2CH_2$$

or by ethyl migration to give N-fluoro-N-ethylethylidenimonium ion.

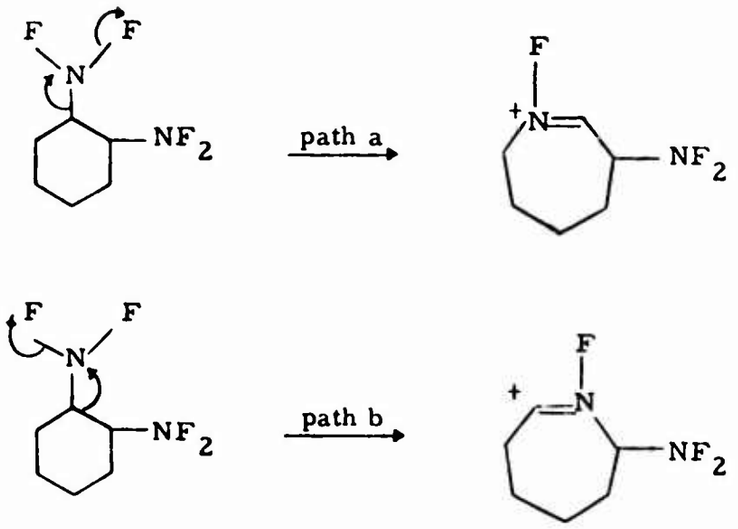
$$CH_3CHNF_2CH_2CH_3 \longrightarrow CH_3CH_2\overset{\oplus}{N}F = CHCH_3$$

The nmr spectra of a solution prepared by shaking 2-difluoraminobutane with sulfuric acid supported the latter reaction product.[10]

Cycloalkyldifluoramines rearranged in the same manner in concentrated sulfuric acid to give cyclic fluorimonium ions by ring expansion.[8] Difluoraminocyclohexane, 1-difluoramino-1-methylcyclohexane, and difluoraminocyclopentane rearranged as shown below.

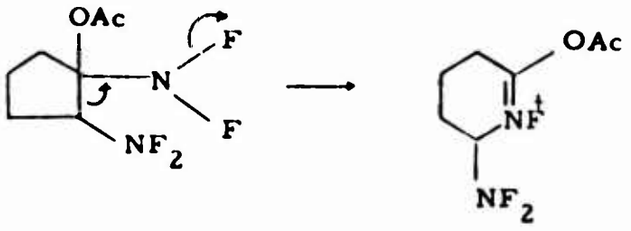


In the reaction of 1, 2-bis(difluoramino)cyclohexane with acids, either the methylene group (path a) or the difluoraminomethylene group (path b) could take part in migration to the electron-deficient nitrogen. Actually, the nmr spectra of the solution formed from 1, 2-bis(difluoramino)-cyclohexane and sulfuric acid were quite complex and relative peak heights changed while the spectrum was being recorded. Apparently, hydrolytic degradation of the rearrangement product took place. This problem was avoided by using fluorosulfonic acid in place of sulfuric acid. Although a violent reaction took place when 1, 2-bis(difluoramino)cyclohexane was

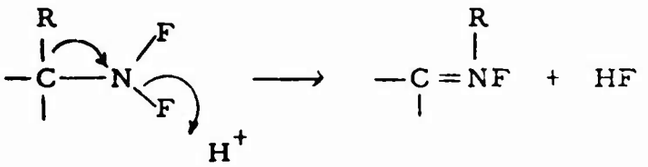


added dropwise to this acid at 0°, the reaction proceeded smoothly when the acid was cooled to -78°. The solution formed was stable at room temperature. The nmr spectra of the fluorosulfonic acid solution showed that path a was followed. The difluoraminomethylene group has a smaller migratory aptitude than the unsubstituted methylene.

This result is contrary to the directing influence of a difluoramino group in the reaction of 1, 2-bis(difluoramino)-1-acetoxycyclopentane with acids to give 3-difluoramino-2-fluoro-2-azacyclohexanone, reported by Stevens and Graham."



This sensitivity to structural features is consistent with a nucleophilic migration mechanism.



The observed relative migratory aptitude of alkyl groups in monofunctional difluoramines - in particular, the failure of methyl groups to migrate when another group is available - is indicative of a transition state in which positive charge resides on the migrating group. This effect has been discussed with respect to the Baeyer Villiger rearrangement.[12] The difluoramino group has been shown to be electron-withdrawing in nitrogen trifluoride, difluoramine, and difluoraminoethane, with a group electronegativity of about 3.25[13]. On the other hand, the unshared pair of electrons on nitrogen is available to stabilize cations, such as $NF_2O^{\oplus}$[14] and $NF_2{=}NF^{\oplus}$[15]. Small changes in structure might thus result in reversals of relative migratory aptitude between an unsubstituted migrating group and a similar one containing a difluoramino group, since the difluoramino group is thus similar to halogens in its diversity of electronic responses.

V. CARBONYL COMPOUNDS

Freeman, Graham, and Parker[16] found that difluoramine adds reversibly to aliphatic ketones and aldehydes to give α-difluoramino-carbinols. Formaldehyde, acetaldehyde, butyraldehyde, benzaldehyde, acetone, cyclohexanone, diethyl ketomalonate, and 3-hydroxy-3-methyl-butanone-2 were used. The adducts of simple aldehydes were sufficiently stable for analysis and adducts of ketones were identified spectrally and, in the case of diethyl ketomalonate, by etherification with diazomethane.

$$R-\underset{\underset{O}{\|}}{C}-R' + HNF_2 \longrightarrow R-\underset{\underset{OH}{|}}{\overset{\overset{NF_2}{|}}{C}}-R'$$

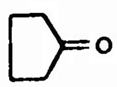
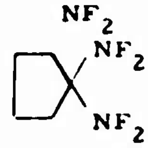
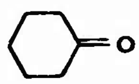
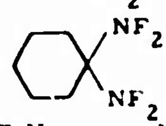
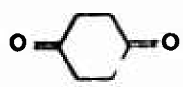
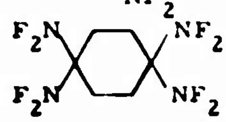
Concentrated sulfuric acid converted difluoraminomethanol to α,α'-bis(difluoraminomethyl)ether.

$$NF_2CH_2OH \xrightarrow{H^+} NF_2CH_2^{\oplus} \longrightarrow F_2N^{\oplus}=CH_2$$

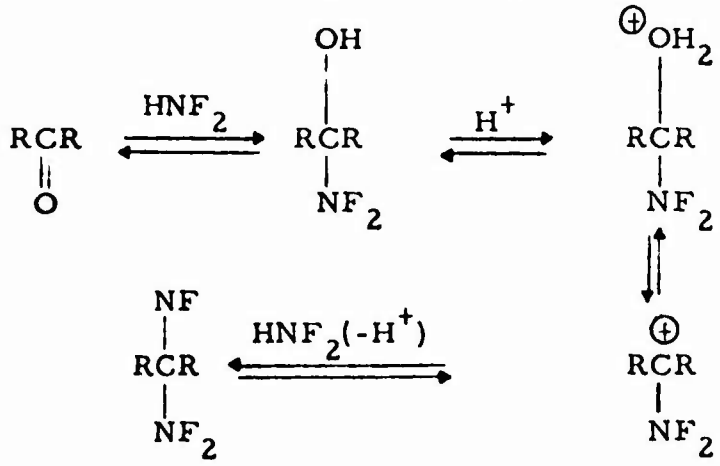
$$\xrightarrow{NF_2CH_2OH} O(CH_2NF_2)_2$$

It was found subsequently[17] that carbonyl compounds can react further with difluoramine in sulfuric acid to give gem-bisdifluoramines. Examples of the conversion of ketones to bisdifluoramines are shown in Table I.

TABLE I. gem-Bis(difluoramino) Derivatives of Ketones

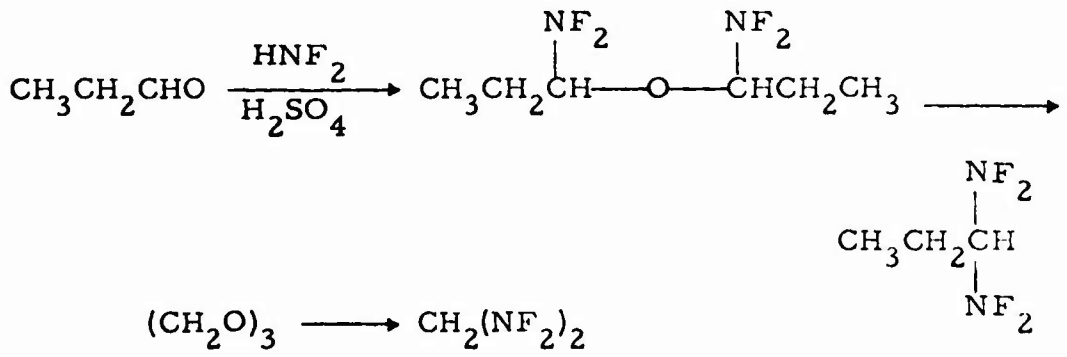
Starting material	Product
$CH_3C(=O)CH_3$	$CH_3C(NF_2)_2CH_3$
$C_2H_5C(=O)C_2H_5$	$C_2H_5C(NF_2)_2C_2H_5$
$CH_3C(=O)(CH_2)_5CH_3$	$CH_3C(NF_2)_2(CH_2)_5CH_3$
	
	
	
$ClCH_2C(=O)CH_3$	$ClCH_2C(NF_2)_2CH_3$
$CH_3C(=O)(CH_2)_3CO_2C_2H_5$	$CH_3C(NF_2)_2(CH_2)_3CO_2C_2H_5$
$CH_3C(=O)(CH_2)_3NO_2$	$CH_3C(NF_2)_2(CH_2)_3NO_2$
$CH_3C(=O)CH_2CH_2C(NO_2)_2CH_3$	$CH_3C(NF_2)_2CH_2CH_2C(NO_2)_2CH_3$
$CH_3C(=O)CH_2CH_2C(NO_2)_3$	$CH_3C(NF_2)_2CH_2CH_2C(NO_2)_3$

Simple ketones reacted readily with a mixture of concentrated sulfuric acid and refluxing difluoramine (bp -23°), although no reaction took place with sulfuric acid of less than 92% concentration. Electron-withdrawing substituents required more forcing conditions, such as a more acidic medium (oleum) or a higher reaction temperature (attained by using a closed reactor). The sequence leading to bis(difluoramino)alkanes was shown to be reversible; 2-octanone was recovered when 2, 2-bis(difluoramino)-octane was shaken with sulfuric acid for 1 hr at room temperature. Yields of bis(difluoramino)alkanes are therefore affected by any variables involved in the rates of the individual steps in the equilibria:



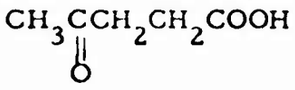
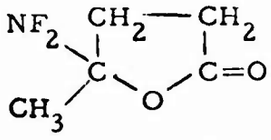
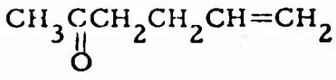
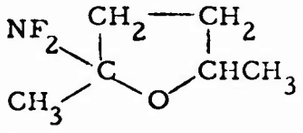
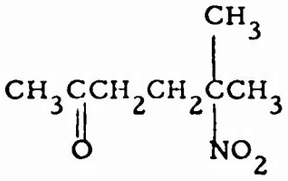
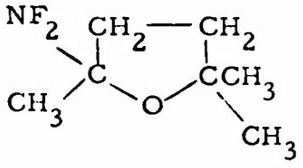
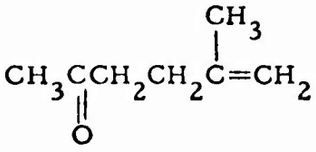
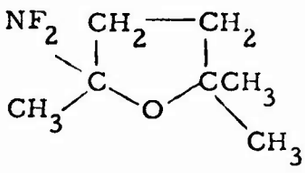
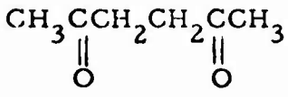
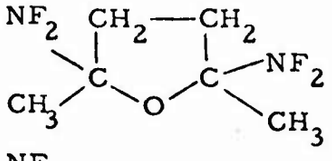
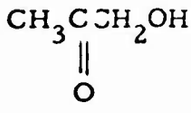
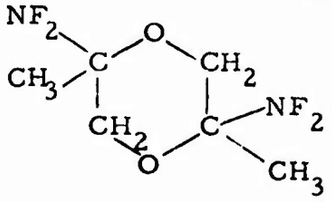
In general, a high concentration of difluoramine, a solvent with a strong affinity for water, and a low solubility for the product are favorable factors. The importance of reaction conditions in the case of 5, 5, 5, -trinitro-2-pentanone is illustrative. No reaction took place with refluxing difluoramine and concentrated sulfuric acid in 4 hr. Using 100% sulfuric acid, 4 ml/mmol of ketone, and an eightfold excess of difluoramine at room temperature gave a 53% conversion in 40 hr, and starting material was recovered. Using 20% fuming sulfuric acid, only 0. 7 ml/mmol of ketone, and a threefold excess of difluoramine at its reflux temperature gave a 99. 5% yield in only 2 hr.

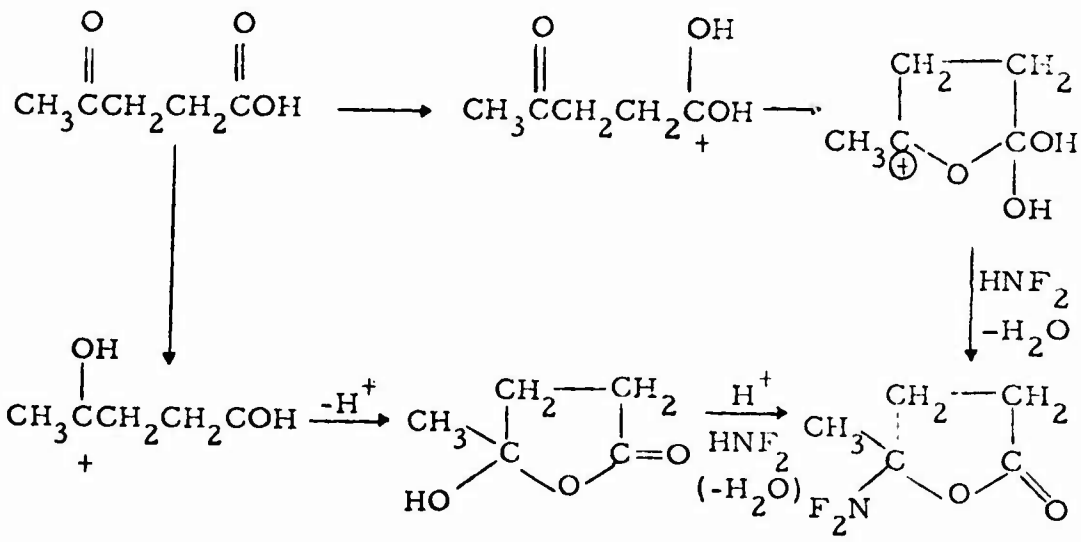
Aldehydes were also converted to bis(difluoramino)alkanes, but more forcing conditions were required than for simple ketones. n-Propionaldehyde gave 1, 1-bis(difluoramino)propane, and α, α'-bis(difluoramino)propyl ether was isolated as an intermediate. Trioxane similarly was converted to bis(difluoramino)methane, which was characterized by nitrogen analysis and infrared spectra. Further characterization of bis(difluoramino)methane was restricted by its extreme sensitivity; explosions occurred during vacuum line manipulations.



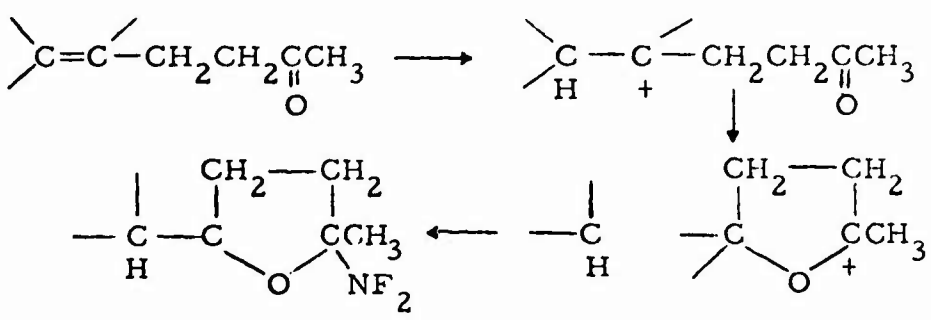
Carbonyl compounds with carbonium ion precursors in suitable positions gave difluoramino-substituted lactones, tetrahydrofurans, and dioxanes. The reactions listed in Table II were carried out in the presence of refluxing difluoramine, using concentrated sulfuric acid as the solvent. These reactions can be rationalized as difluoramine alkylations by the carbonium ions which result from intramolecular alkylation of carbonyl groups. In the case of levulinic acid, the same product would be formed by the protonation of either the carboxyl or keto carbonyl groups:

TABLE II. Cyclization Reactions

Starting material	Product
	
	
	
	
	
	

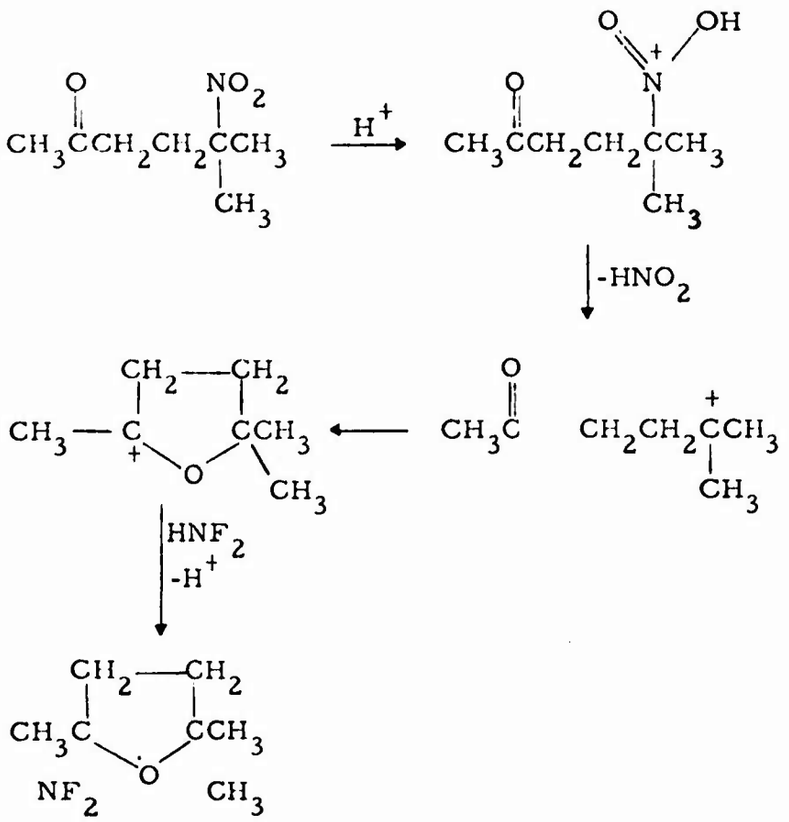


For the olefinic starting materials in Table II, the observed products can arise only by protonation of the olefinic bonds; initial attack on the carbonyls would give carbocyclic products.

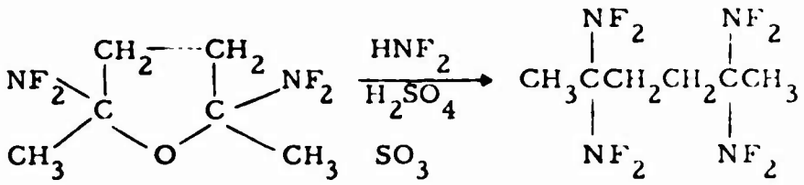


Some similar acid-catalyzed cyclization and addition reactions have been reported for reagents other than difluoramine. For example, the acetylation of levulinic acid was reported to give 4-acetoxy-4-methylbutyrolactone.[18] Tetrahydrofuran derivatives were formed by the acid-catalyzed ring closure of both 4-hydroxy olefins, and 5-hydroxy olefins.[19] Also, γ-hydroxyaldehydes[20] have been reported to give 2-alkoxytetrahydrofurans on reaction with alcohols. The reaction of acetol with alcohols gave 2, 5-dialkoxy-2, 5-dimethyl-1, 4-dioxanes.[21]

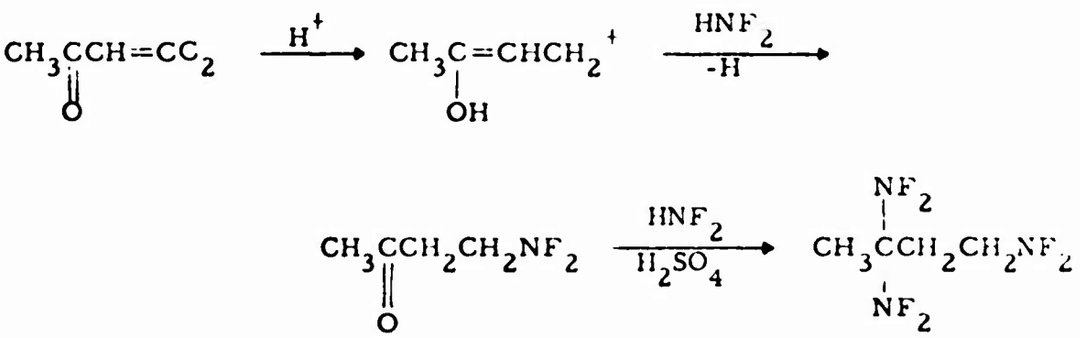
The reaction of 5-methyl-5-nitro-2-hexanone is explainable on the basis of protonation of an oxygen atom of the nitro group followed by loss of nitrous acid and intramolecular alkylation of the carbonyl oxygen. Recent nmr studies[22] have shown that primary nitroalkanes are protonated reversibly in strong acids, whereas α-nitrobutane gives the α-butyl cation.



In a prolonged reaction of acetonylacetone with difluoramine in fuming sulfuric acid at room temperature, ring opening of the initially formed tetrahydrofuran derivative took place, and 2, 2, 5, 5-tetrakis(difluoramino)hexane was prepared. In this experiment, some acetonylacetone was recovered, although none was found when the tetrahydrofuran derivative was prepared under milder conditions.



Methyl vinyl ketone underwent an initial Michael addition of difluoramine with subsequent replacement of the carbonyl to give 1, 3, 3-tris(difluoramino)-butane.

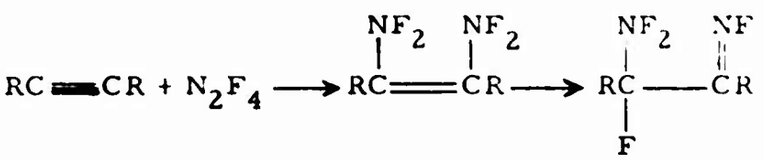


Other examples of the Michael reaction of difluoramine were demonstrated using acrylic acid and methyl acrylate; β-(difluoramino)propionic acid and methyl β-(difluoramino)propionate, respectively, were isolated. Acrylonitrile, however, did not react under these conditions.

Since simple primary, secondary, and tertiary alkyldifluoramines rearrange rapidly in sulfuric acid to give fluorimmonium ions, the question arises as to why the products observed here survived reaction times of up to several days under essentially the same conditions. Protonation of oxygen-containing products would inhibit the formation of another cationic center by rearrangement. The inductive affect of difluoramino groups of gem-bis-(difluoramino)alkanes would likewise give a lower electron density on the adjacent carbon than for the simple derivatives.

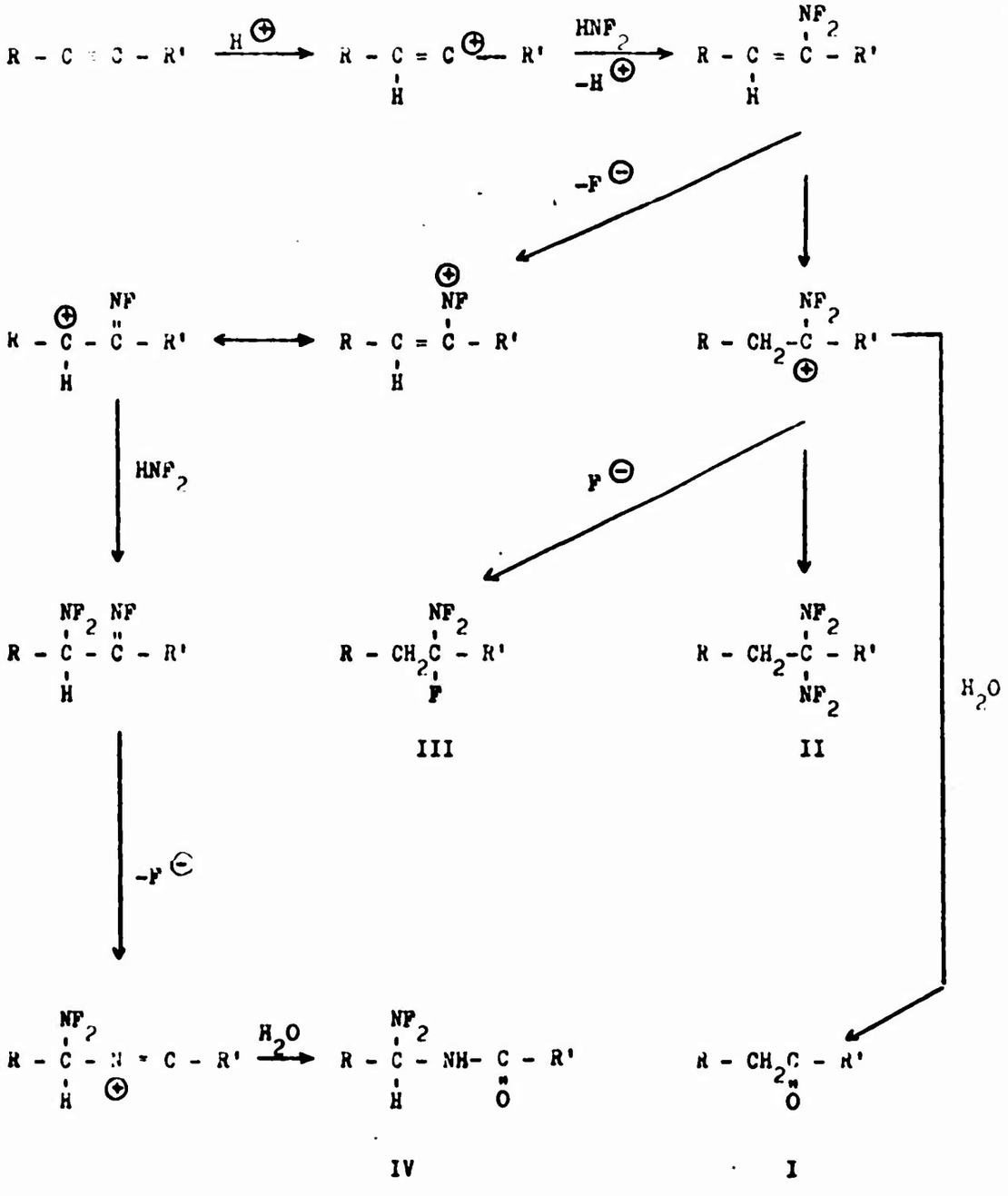
VI. ACETYLENES

The addition of tetrafluorohydrazine to acetylenes has been reported to take place with the formation of vicinal bis(difluoroamino)ethylenes, followed by pseudoallylic fluorine migration.[23,24] It was possible to isolate the unrearranged adduct only in the case of perfluoroalkyl acetylenes.[24]



The reaction of difluoramine with an acetylene would be expected to give a vinyldifluoramine as the initial adduct under mild conditions, and the ultimate products would reflect the chemical properties of this moiety. This reaction was studied using the boron trifluoride complex of phosphoric acid or sulfuric acid as catalyst.[25]

Difluoramine reacted at its reflux temperature with 3-hexyne in the presence of the boron trifluoride complex of phosphoric acid. The volatile products, separated by gas chromatography, were identified as 3-hexanone (Ia), 3,3-bis(difluoramino)hexane (IIa), and 3-difluoramino-3-fluorohexane (IIIa). When the nonvolatile residue containing the catalyst was quenched with water, a solid (mp 50-51.5°) was obtained identified as N-(α-difluoramino-propyl)-propionamide (IVa). The analogous products, 2-hexanone (Ib), 2,2-bis(difluoramino)hexane (IIb), 2-difluoramino-2-fluorohexane (IIIb), and N-(difluoraminomethyl)valeramide (IVb), were obtained from 1-hexyne. The observed products can be rationalized as follows:



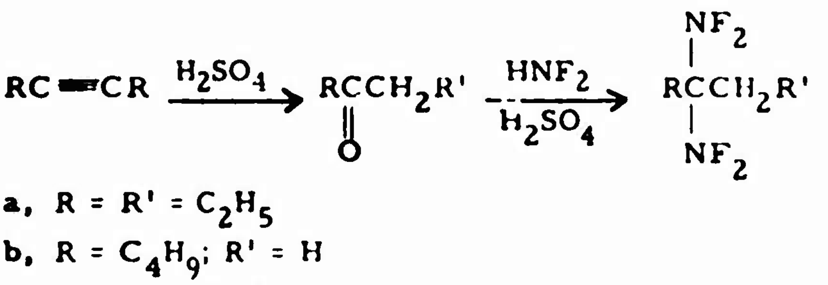
a. $R = R' = C_2H_5$

b. $R = H$, $R' = C_4H_9$

Protonation of the acetylene followed by alkylation of difluoramine would give the vinyldifluoramine. Further protonation would give the difluoramino-carbonium ion, which could alkylate difluoramine to give II or fluoride to give III. An alternative path for the formation III is the addition of diluoramine to the fluoro olefin resulting from the addition of HF to the original acetylene. The ketone could result from hydration of the original acetylene or of the difluoraminocarbonium ion; ketones were not converted to bisdifluoramino compounds under these reaction conditions. The loss of fluoride ions from the vinyldifluoramine would give a mesomeric cation, capable of alkylating difluoramine. Beckmann rearrangement of the resulting fluorimine would then give IV.

The fact that no vicinal bis(difluoramino)alkanes were isolated is evidence of the ability of the difluoramino group, as a pseudohalogen, to stabilize a carbonium ion center.

Acetylenes also reacted with difluoramine in the presence of concentrated sulfuric acid, but the only products isolated were gem-bis(difluoramino)-alkanes. Thus, 1-hexyne, 3-hexyne, and propargyl chloride gave 2,2-bis-(difluoramino)hexane, 3,3-bis(difluoramino)hexane, and 1-chloro-2,2-bis-(difluoramino)propane, respectively. A control experiment indicated that under these conditions ketones formed by acetylene hydration were intermediates.



a, $R = R' = C_2H_5$

b, $R = C_4H_9$; $R' = H$

c, $R = CH_2Cl$; $R' = H$

VII. DIAZONIUM IONS

Aryldiazonium ions couple to simple amines to give triazenes, whereas coupling products to nitrogen compounds with labile substituents, such as chloramine or hydroxylamine, undergo α-elimination to give aryl azides. Fluorocarbamates were also found to react with diazonium salts,[26] but only in the presence of a mild base such as potassium fluoride or pyridine. Isopropyl fluorocarbamate and benzenediazonium fluoborate gave phenyl azide and isopropyl fluoroformate as the major products, as well as diisopropyl N-fluoriminodicarboxylate. Other diazonium fluoborates gave similar reactions.

The formation of aryl azides by this reaction represents another example of diazonium coupling to a nitrogen compound with α-elimination, the first such example in which an acyl halide is eliminated. Diisopropyl N-fluoriminodicarboxylate was most likely formed from the reaction of isopropyl fluoroformate with isopropyl fluorocarbamate.

$$ArN_2^+BF_4^- + HNFCO_2R + \text{base} \longrightarrow$$

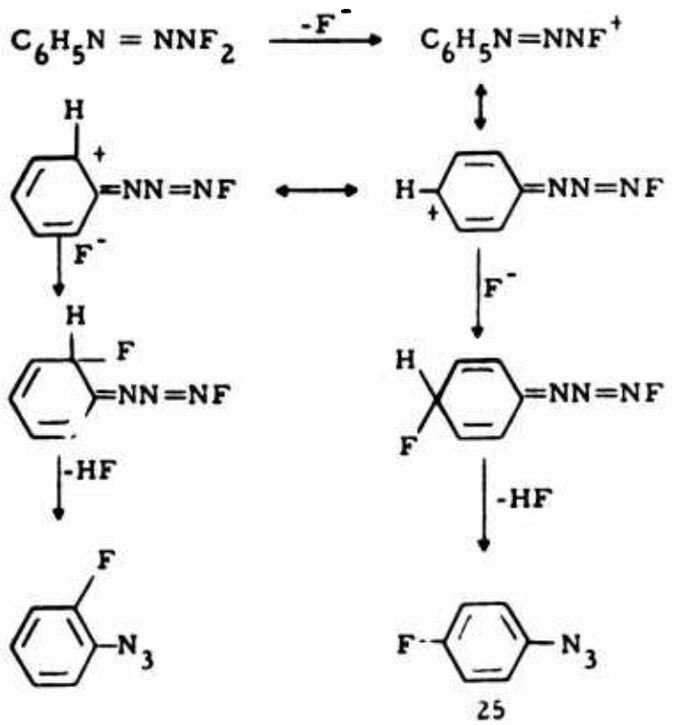
$$ArN{=}NNCO_2R + \text{base}\cdot HBF_4$$

$$ArN{=}NNCOR \longrightarrow ArN_3 + FCOR$$

$$ROCNHF + ROCF \longrightarrow ROCNCOR$$

Benzenediazonium fluoroborate, which has low solubility in common solvents, including water, was found to be very soluble in liquid difluoramine. The addition of pyridine or potassium fluoride to remove fluoroboric acid resulted in the formation of o-fluorophenyl azide, p-fluorophenyl azide, and benzene. These azides, as well as the meta isomer, were synthesized independently. Yields in the difluoramine reaction were variable, and considerable amounts of tars were formed. In several instances two unidentified products were formed with ^{19}F signals indicative of NF compounds; a 1:1:1 triplet at ϕ^* -32.5 and a broadened singlet at ϕ^* -26.2

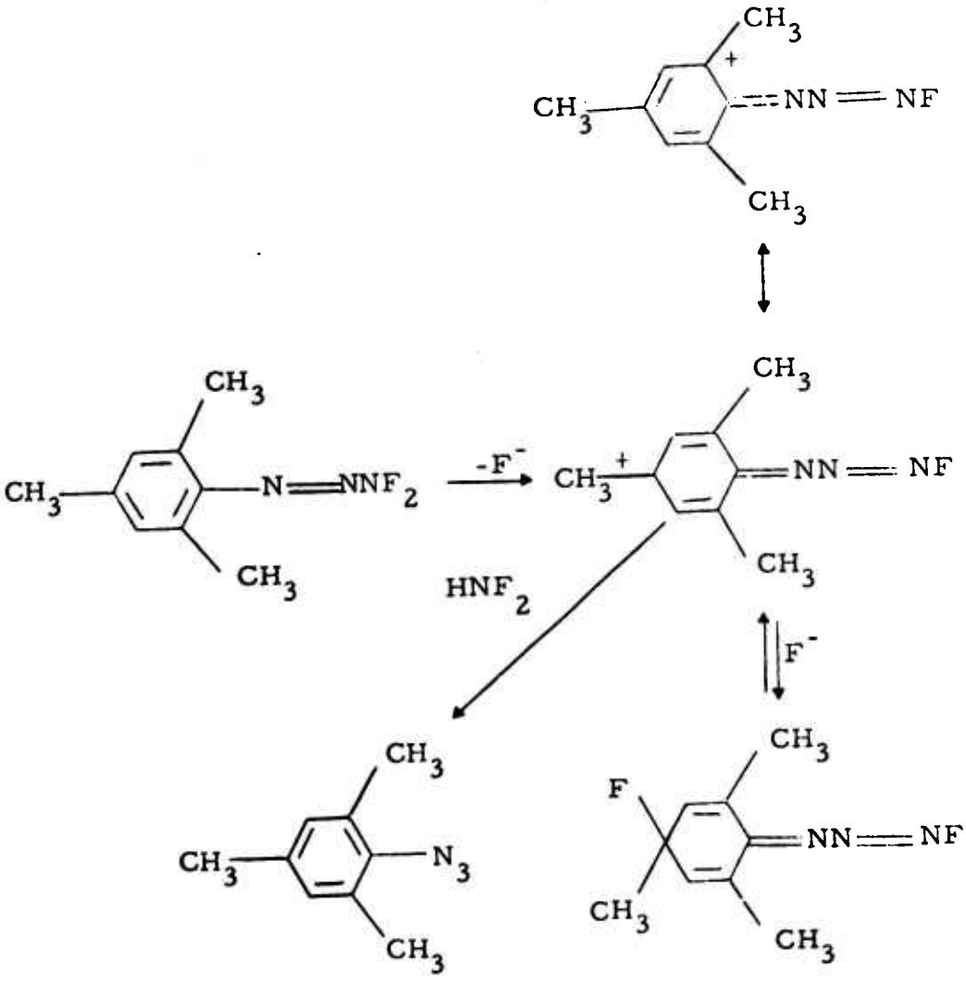
o-Fluorophenyl azide and p-fluorophenyl azide could be formed from the expected coupling product, 1-phenyl-3, 3-difluorotriazene, by loss of fluoride ion to give a resonance-stabilized cation having carbonium ion character at the ortho and para positions. The addition of fluoride at these positions would give semi-quinoid intermediates which would give the observed fluoro azides by the elimination of HF. The absence of the meta isomer is consistent with this mechanism.



Diazonium salt reductions generally take place by a homolytic mechanism, and the above difluorotriazene would be expected to react readily in this manner by loss of the stable difluoramino radical. The resulting diazoaryl or aryl radicals could abstract hydrogen from difluoramine to give benzene.

Blocking the ortho and para positions of the diazonium salt with methyls should alter the above path in two ways. The diazonium coupling product should lose fluoride more readily because of methyl stabilization of positive charge in the ring. Homolytic decomposition should therefore consume a smaller portion of the intermediate. However, addition of fluoride ion to ortho or para positions in the cation cannot lead to fluoro azides without the rupture of a C-C bond, so this step should be reversible.

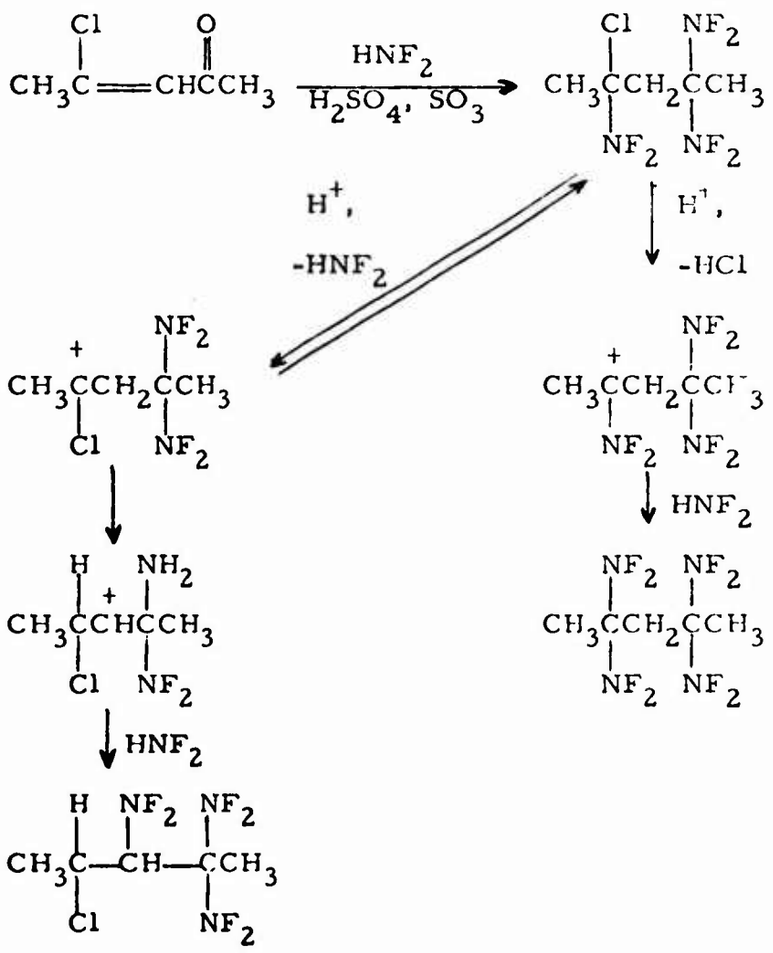
The reaction of 2,4,6-trimethylbenzenediazonium fluoroborate with difluoramine in the presence of potassium fluoride was found to give an 86% yield of 2,4,6-trimethylphenyl azide and a trace of mesitylene. The formation of 2,4,6-trimethylphenyl azide could take place by loss of fluoride from the triazene, followed by aromatization by loss of electropositive fluorine to an available fluorination substrate, i.e., difluoramine.


CH3
+
CH3
NN
NF
CH3
CH3
N
NNF2
-F-
CH3
+
CH3
NN
NF
CH3
HNF2
F-
CH3
CH3
N3
CH3
CH3
F
NN
NF
CH3
CH3

VIII. HALOGEN COMPOUNDS

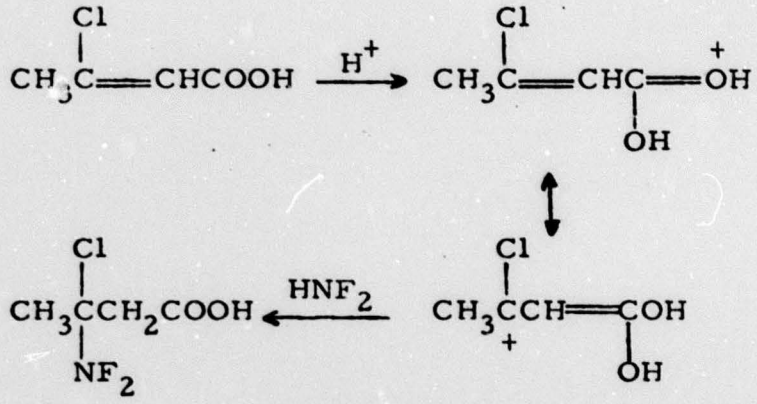
Extension of the study of reactions of α, β-unsaturated carbonyl compounds[17] to halogenated substrates[27] resulted in the observation of some unusual rearrangements, as well as halogen substitution, 1,4-additions and carbonyl substitutions. The first example of the alkylation of difluoramine by an α-halo difluoramino compound was observed by Graham and Freeman,[28] who obtained a low yield of 2,2-bis(difluoramino)propane from 2-chloro-2-(difluoramino)propane and difluoramine in sulfuric acid.

2-Chloro-2-penten-4-one[27] was found to react with difluoramine and fuming sulfuric acid to give 2,2,4-4-tetrakis(difluoramino)pentane, 2-chloro-2,4,4-tris(difluoramino)pentane, and 2-chloro-3,4,4-tris(difluoramino-pentane. The expected product of Michael addition of difluoramine to 2-chloro-2-penten-4-one is 2-chloro-2-difluoramino-4-pentanone, and replacement of the carbonyl group with two difluoramino groups would give 2-chloro-2,4,4-tris(difluoramino)-pentane. Ionization of chloride ion from this product and alkylation of difluoramine by the resulting carbonium ion would give 2,2,4,4-tetrakis(difluoramino)-pentane. The formation of 2-chloro-3,4,4-tris(difluoramino)pentane can be rationalized on the basis of a 1,2-hydride shift in a chlorocarbonium ion followed by alkylation of difluoramine by the resulting secondary carbonium ion.

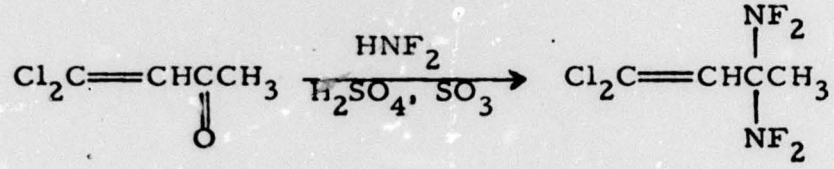


The reaction of cis-3-chlorocrotonic acid with difluoramine in the presence of fuming sulfuric acid gave the Michael adduct, 3-chloro-3-(difluoramino)-butyric acid, in 59% yield. Ethyl 3-chlorocrotonate, on the other hand, did not react under these conditions, and the starting material was recovered. The stability of 3-chloro-3-(difluoramino)butyric acid in sulfuric acid, and the failure of chlorine to leave, is attributed to protonation of the carboxy group; subsequent chloride ionization would give a doubly charged cation. Failure of ethyl 3-chlorocrotonate even to add difluoramine is probably due to the greater

stability of the protonated starting material, rendering the carbonium-ion center unreactive.

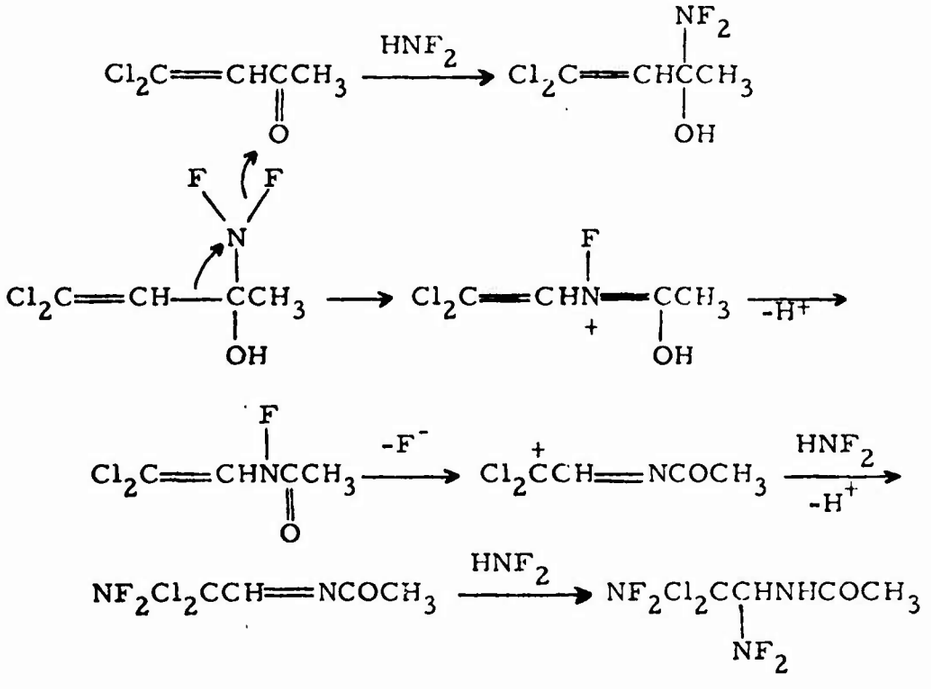


The reaction of 1,1-dichloro-1-buten-3-one with difluoramine took two entirely different courses, depending upon the conditions. In the presence of fuming sulfuric acid and such a large excess of liquid difluoramine that the latter was essentially the solvent (weight ratio of substrate/difluoramine/acid, 1:9:6.3), 1-1-dichloro-3,3-bis(difluoramino)1-butene was isolated in 57% yield.



When this reagent ratio was changed to 1:1.3:6.2, no 1,1-dichloro-3,3-bis(difluoramino)-1-butene was obtained, but a product identified as N-[2,2-dichloro-1,2-bis(difluoramino)ethyl] acetamide was isolated in 24% yield. This product could be formed from the difluoraminocarbinol resulting from addition of difluoramine to the carbonyl group. Loss of fluoride and

migration of the vinyl group would give a fluorimonium ion, which is also a protonated N-fluoroamide. Ionization of the "allylic" fluorine of the latter and the alkylation of difluoramine by the resulting carbonium ion center would give 1,1-dichloro-1-difluoramino-2-N-acetyliminoethane. The addition of difluoramine would then give N-[2,2-dichloro-1,2-bis(difluoramino)ethyl]-acetamide. The high mobility of vinyl groups in nucleophilic rearrangements serves to make rearrangement of the carbinol competitive with hydroxyl removal. The ionization of the "allylic" fluorine of the resulting N-fluoroamide is similar to that of vinyldifluoramines formed by the addition of tetrafluorohydrazine or difluoramine to acetylenes. In the presence of a high concentration of difluoramine, removal of the hydroxyl group of the difluoraminocarbinol and alkylation of difluoramine to give the geminal derivative is favored.



The ability of a dichlorovinyl group to undergo difluoramine addition and of the adduct to undergo substitution of chlorine was demonstrated using a simpler substrate. The reaction of difluoramine and fuming sulfuric acid with 1,1-dichloroethylene at the reflux temperature of difluoramine gave an 8% yield of 1,1-dichloro-1-(difluoramino)ethane. When the reaction was conducted in a closed reactor at ambient temperature for a prolonged period, a mixture of 1,1-dichloro-1-(difluoramino)ethane (7.2% yield) and 1-chloro-1,1-bis(difluoramino)ethane (3.3% yield) was obtained. Further extension of the reaction time, however, did not result in replacement of the remaining chlorine.

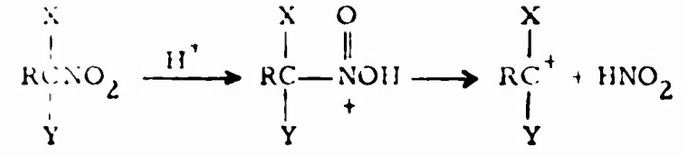
$$CH_2{=}CCl_2 \longrightarrow CH_3CCl_2NF_2 \longrightarrow CH_3CCl(NF_2)_2$$

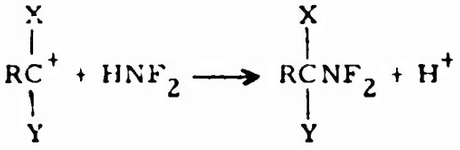
Additional examples of halogen substitution were observed using nitrohalo compounds as starting materials and are described in the following section.

IX. NITRO AND NITROSO COMPOUNDS

The reactions of carbonyl compounds with difluoramine discussed above include several examples with nitro substituents. 5-Nitro-2-pentanone, 5,5-dinitro-2-hexanone, and 5,5,5-trinitro-2-pentanone gave the corresponding gem-bis(difluoroamino)alkanes with nitro groups intact, but the nitro group of 5-methyl-5-nitro-2-hexanone functioned as a carbonium ion precursor. This reaction was examined more thoroughly as a source of carbonium ions for the alkylation of difluoramine.[29]

1,1-Dihalo-1-nitroalkanes were found to react readily with difluoramine and fuming sulfuric acid to give 1,1-dihalo-1-(difluoramino)alkanes. Thus, 1,1-dichloro-1-(difluoramino)butane, 1,1-dibromo-1-(difluoramino)butane, 1-bromo-1-difluoramino-1-fluoropropane, and α,α-dibromo-α-(difluoramino)-toluene were prepared from 1,1-dichloro-1-nitrobutane, 1,1-dibromo-1-nitrobutane, 1-bromo-1-fluoro-1-nitropropane, and α,α-dibromo-α-nitro-toluene, respectively, in yields of 33-61%. Transient blue-purple colorations in the solutions were indicative of nitrosyl difluoramine, formed by the nitrosation of difluoramine. Nitrosyl difluoramine has been prepared reversibly from NO and N_2F_4 at low temperatures.[30] 1,1,1-Bromodinitroalkanes and chlorodinitroalkanes did not react with difluoramine in fuming sulfuric acid. 1-Iodo-1-nitrocyclohexane was degraded under these conditions, but did not react with neat difluoramine.

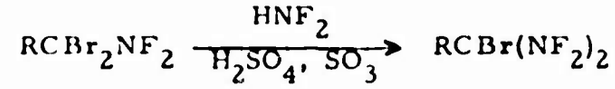




R = C_3H_7; X = Y = Cl
R = C_3H_7; X = Y = Br
R = C_2H_5; X = Br; Y = F
R = C_6H_5; X = Y = Br

Of the above 1-difluoramino-1,1-dihaloalkanes, only the dibromo derivatives were found to undergo halogen substitution. In fact, to obtain a sample of 1,1-dibromo-1-(difluoramino)butane free of the bis(difluoramino)-derivative, it was necessary to quench the reaction (conducted at -10 to -20°) within 10 min. The other compounds did not give difluoramine substitution with reaction times as long as 4 days.

The greater reactivity of 1,1-dichloro-1-(difluoramino)ethane compared with the butane and toluene analogs must be attributed to steric factors.

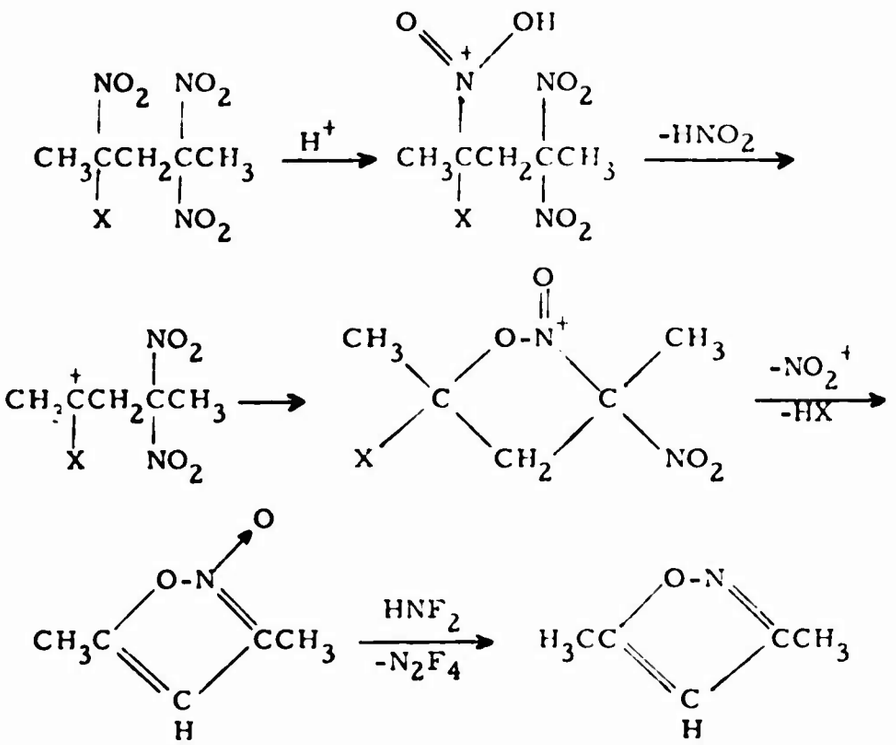


R = C_3H_7, C_6H_5

The only examples of difluoramine reactions in which gem-dinitro groups were replaced involved 2-halo-2,4,4-trinitropentanes. The chloro and bromo

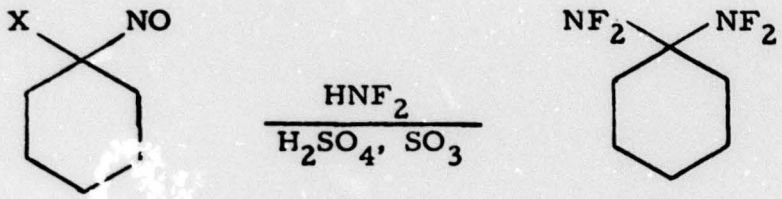
compounds both reacted with difluoramine in fuming sulfuric acid to give the same products, 2, 2, 4, 4-tetrakis(difluoramino)pentane (5-8% yield) and 3, 5-dimethylisoxazole (26-34% yield). Even when reaction conditions were used that resulted in the recovery of some unreacted starting materials, no other products were isolated. The isoxazole also gave 2, 2, 4, 4-tetrakis(difluoramino)pentane.

A possible path for the formation of 3, 5-dimethylisoxazole is shown below.



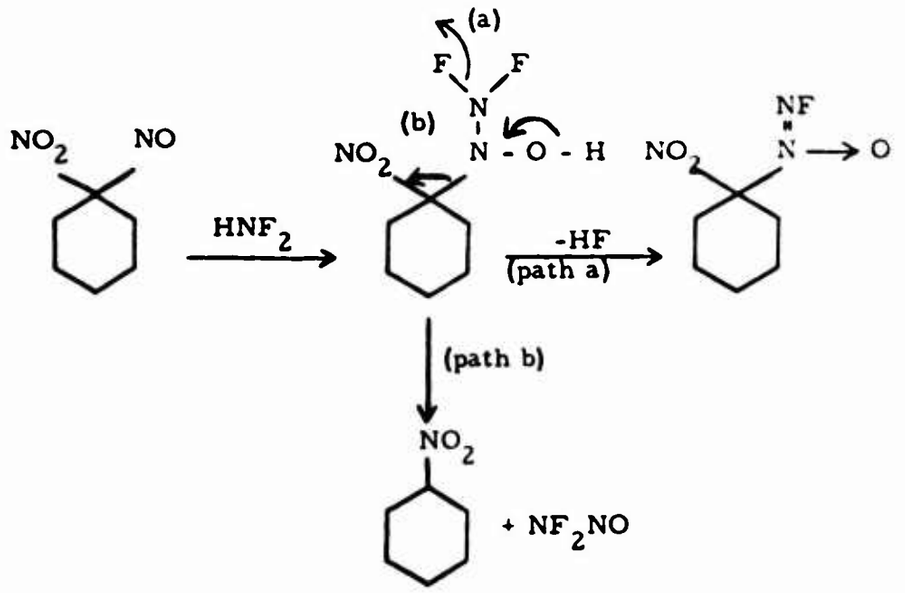
Protonation of the most basic nitro group and loss of nitrous acid would give a halocarbonium ion. Intramolecular alkylation of the oxygen of a nitro group, followed by loss of nitronium ion and HX would give 3, 5-dimethylisoxazole N-oxide, which could be reduced to the isoxazole by difluoramine.

Nitroso compounds react with difluoramine in the presence of pyridine to give N'-fluorodiimide N-oxides.[31] Under acidic conditions, nitroso compounds were also found to be useful alkylating agents for difluoramine. Thus, the only product isolated from the reactions of 1-chloro-1-nitrosocyclohexane or 1-nitro-1-nitrosocyclohexane with difluoramine and fuming sulfuric acid was 1,1-bis(difluoramino)cyclohexane, even when the reaction, in the latter case, was quenched within 5 min.

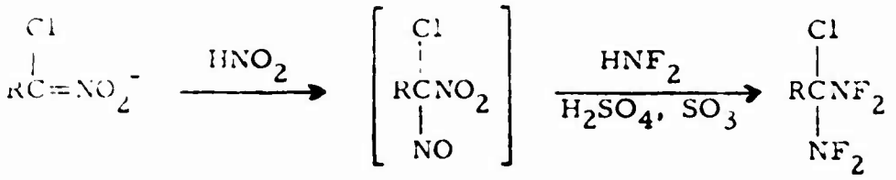


X = Cl or NO_2

With the objective of isolating possible intermediates, the reaction of 1-nitro-1-nitrosocyclohexane with difluoramine was repeated using a more selective catalyst, the boron trifluoride complex of phosphoric acid. Under these conditions, 1,1-bis(difluoramino)cyclohexane was not formed, but nitrocyclohexane and 1-nitrocyclohexyl-N'-fluorodiimide N-oxide were isolated. These products could be formed from a common intermediate, the adduct of difluoramine to the N=O bond, by cleavage of either the N-F or the C-N bond.



A sample of 1-nitrocyclohexyl-N'-fluorodiimide N-oxide was treated with difluoramine in fuming sulfuric acid to determine if this compound could be an intermediate in the formation of 1,1-bis(difluoramino)cyclohexane. The unchanged starting material was recovered. The reaction thus appears to involve initial solvolysis of a protonated nitro or nitroso group, or of the hydroxylamine function postulated above. When one group is replaced, the remaining one becomes sufficiently reactive that intermediates are not isolated. Unstable 1-chloro-1-nitro-1-nitrosoalkanes were used to prepare 1-chloro-1,1-bis-(difluoramino)alkanes not obtainable from the dichloronitroalkanes. Nitrosation of aqueous solutions of the sodium salts of 1-chloro-1-nitropropane and 1-chloro-1-nitrobutane at 0^{o} gave dark blue oils which reacted with difluoramine in fuming sulfuric acid to give 1-chloro-1,1-bis(difluoramino)-propane and 1-chloro-1,1-bis(difluoramino)butane, respectively.



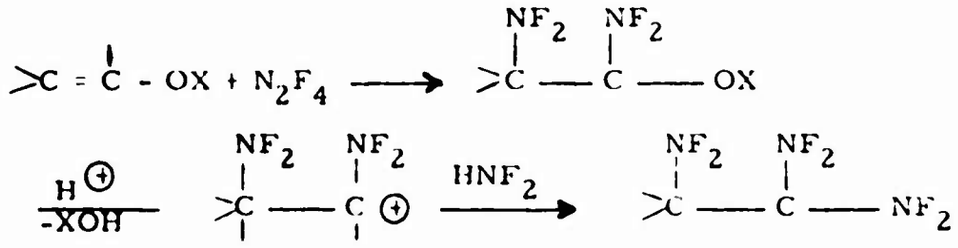
$R = C_2H_5$ or C_3H_7

Octyl nitrite reacted with liquid difluoramine to give a blue-purple solution indicative of nitrosyldifluoramine. Removal of the difluoramine left n-octanol. No catalyst was necessary for this reaction. The nitrite thus acted as a nitrosation agent rather than an alkylating agent toward difluoramine.

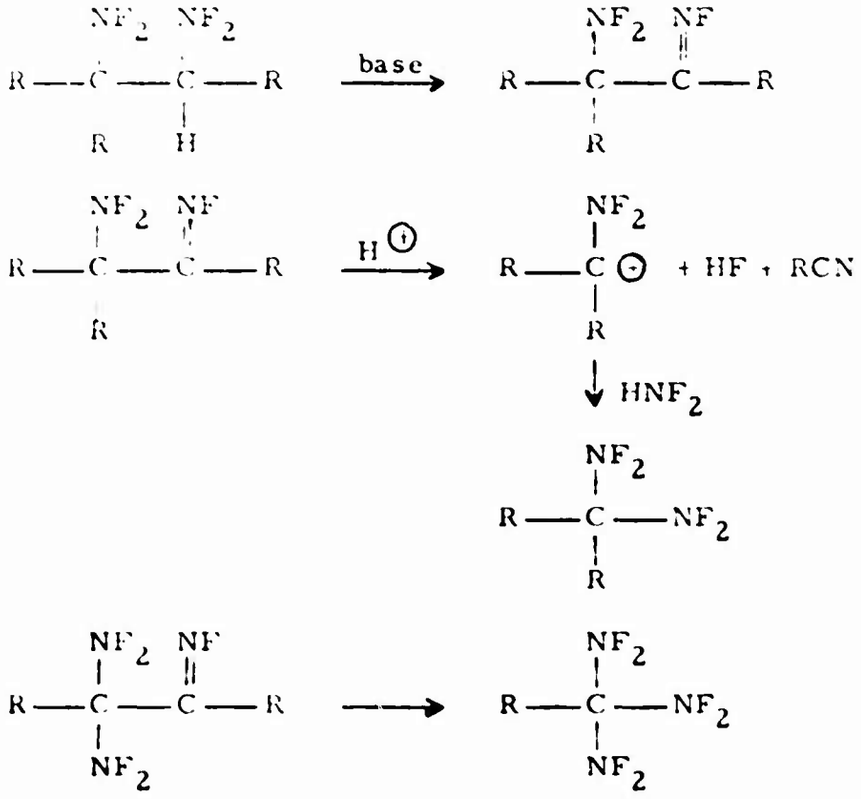
$$RONO + HNF_2 \longrightarrow ROH + NONF_2$$

X. TRIS(DIFLUORAMINO)ALKANES

Tetrafluorohydrazine additions to olefins have been used to prepare intermediates for the generation of carbonium ions α or β to difluoramino groups. Thus, Freeman, Petry and Stevens[32] prepared α, β-bis(difluoramino)-alkyl acetates and phosphates by the addition of N_2F_4 to the corresponding enol esters. These adducts reacted with difluoramine in sulfuric acid to give 1,2,2-tris(difluoramino)alkanes.



Stevens made extensive use of the Beckmann fragmentation of fluorimines to generate carbonium ion centers α to difluoramino groups. α-Difluoraminofluorimines were prepared by dehydrofluorination of vicinal bis-difluoramines, including 1,2,2-tris(difluoramino)alkanes. Reaction of the fluorimines with difluoramine under strongly acidic conditions gave bis- and trisdifluoramino compounds by fragmentation as well as difluoraminoamides by rearrangement.


base
H⊕
+ HF + RCN
HNF2

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DIRECT LIQUID PHASE FLUORINATION OF ORGANIC COMPOUNDS

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CONTENTS

I. INTRODUCTION

In 1958 we became interested in the synthesis of organic fluorine compounds and surveyed various known fluorination techniques. We associated the fluorination of organic compounds with chlorination and bromination reactions, and in this respect liquid phase fluorination appeared to be the simplest technique. The literature survey, however, indicated that this fluorination technique was by far the least explored[1]. Attempts to fluorinate organic compounds under such conditions led to explosions, firings, and degradation (or polymerization) of substrates. These observations formed the prevailing opinion that direct liquid phase fluorination of organic compounds was not suitable for preparative purposes.

Our interest in the liquid phase fluorination technique was encouraged by the findings of several investigators who successfully employed this technique and whose contributions to the development of fluorine chemistry, in our opinion, were grossly underemphasized and underestimated. Successful fluorination of organic compounds in solution under very mild and simple reaction conditions was reported by Fichter and Brunner[2] in 1929, Bochemuller[3] in 1933, and by Miller[4,5] in 1940. These fluorination reactions, carried out in conventional equipment, proceeded smoothly and selectively. It is difficult to rationalize why the findings of these workers did not encourage further exploration of this simple and elegant fluorination technique, and why so many researchers selected to pursue much more involved and nonselective vapor phase fluorination. The work of Fichter, Bochemuller and Miller

suggested to us that with additional work the liquid phase fluorination of organic compounds could be developed into a practical and general technique. The account of our rewarding efforts toward this objective during the past 12 years is the subject of this summary.

The following discussion opens with a brief description of the fluorination apparatus and the general experimental techniques employed in our work, and is followed by sections dealing with the fluorination of (a) nitrogenous compounds, (b) alkali salts of organic acids, and (c) hydrocarbons.

II. APPARATUS AND GENERAL TECHNIQUES

Direct liquid phase fluorination of organic compounds is a simple procedure and can be performed in the laboratory on a molar scale. The potential dangers of such reactions, however, should not be overlooked. Fluorine is extremely reactive toward organic compounds, and under improper operating conditions direct liquid phase fluorination reactions might lead to serious accidents.

Fluorinations were carried out in glass standard taper three-necked flasks equipped with a mechanical stirrer, a glass inlet tube extending below the liquid level, and a thermometer well with an opening for gas exit. Standard fluorine handling hardware[6] was used, and fluorine was diluted with nitrogen (1:3 to 1:5 ratio).

The apparatus must be scrupulously clean and fluorine must be diluted with an inert gas such as helium or nitrogen. We found that it is convenient to start the fluorination with "lean" fluorine (diluted with nitrogen to 1:6-1:8)

and to increase its concentration as the reaction progresses. Reactions should be started slowly and at low temperatures. Both the rate of fluorination and the reaction temperature can be increased later in the run. The reactor should be shielded and all lines containing fluorine under pressure should be located behind a heavy barricade. It is convenient to incorporate a pressure-calibrated stainless steel cylinder of 500-2000 ml capacity between the fluorine cylinder and the reactor. This cylinder is charged with fluorine and the main fluorine cylinder is closed. The pressure drop in the auxiliary cylinder during the fluorination indicates the amount of fluorine consumed. An important safety consideration is that the main fluorine cylinder is not directly connected to the apparatus.

Water, methanol, acetonitrile, carbon tetrachloride, methylene chloride, perchlorofluoroalkanes, and other solvents and solvent mixtures were used in this work. All these "inert" solvents, with the possible exception of perchlorofluoroalkanes, react slowly with elementary fluorine. However, under actual fluorination conditions in the presence of an even moderately reactive substrate, the rate of fluorination of these solvents is insignificant. Water, acetonitrile, and 1,1,2-trichloro-1,2,2-trifluoroethane were found to be the most useful solvents. Acetonitrile undergoes fluorination to some extent, and on several occasions fluoroacetonitrile was identified in the recovered solvent. In several instances liquid substrates were fluorinated undiluted.

III. FLUORINATION OF ORGANIC NITROGENOUS COMPOUNDS

A. Introduction

The first reported example of the fluorination of a nitrogenous compound in aqueous solution was the synthesis of N, N-difluorourea from urea.[7] Subsequently, these fluorination reactions were extended to substituted ureas, amides and carbamates. The fluorination of all these nitrogenous compounds proceeds stepwise to give the corresponding N-fluoro derivatives, which, on further fluorination, react with the second mole of fluorine yielding difluoro-amino compounds:

$$RNHCOX + F_2 \longrightarrow RNFCOX + HF$$

$$RNFXOC + F_2 \longrightarrow RNF_2 + FCOX$$

R = H or an alkyl group

X = Alkyl, alkoxy, NH_2, or NHR group

In most cases the rates of fluorination in the two steps are of the same order of magnitude placing limitations on the maximum yields of N-fluoro intermediates.

B. Fluorination of Ureas

In 1956 Glemser and Lüdemann[8] reported that fluorination of solid urea gave biurea and postulated that fluorourea was an intermediate in this reaction. Lawton, et al.[9, 10] identified N, N-difluorourea as one of the fluorination products. Because of its importance as difluoramine intermediate in NF chemistry, we became interested in the synthesis of N, N-difluorourea and found that fluorination of aqueous urea is a more readily

controllable reaction. The moderating effect of the solvent allowed the use of simple apparatus and N, N-difluorourea was obtained in 75-80% yields.[7,11] The compound was also prepared by the fluorination of a suspension of urea in acetonitrile.[11]

$$NH_2CONH_2 + F_2 \xrightarrow{H_2O} NF_2CONH_2 + 2\ HF$$

The NH_2 group of N, N-difluorourea is unreactive and further fluorination does not yield more highly fluorinated ureas. N, N-difluorourea, a white crystalline solid, mp 41-41.5°, must be handled with caution. It is a sensitive explosive and is toxic.

The aqueous N, N-difluorourea as obtained in the fluorination can be stored for several days at 0° or for several months at -20° with little decomposition. The solution hydrolyzes readily at 60-90° and this reagent becomes a widely used source of difluoroamine.[7,11-14]

$$NF_2CONH_2 + H_2O \xrightarrow{H_3O^+} HNF_2 + CO_2 + NH_4^+$$

The reaction of N, N-difluorourea with a base has been reported to be a convenient synthesis for difluorodiazine:[13]

$$2\ NF_2CONH_2 + NaOH \xrightarrow{H_2O} N_2F_2 + 2\ NaF$$

N, N-Difluorourea also reacts instantaneously with sulfuric acid solutions of chromates and other oxidizing agents to give tetrafluorohydrazine in excellent yields:[15]

$$2\ NF_2CONH_2 + Cr^{+6} \xrightarrow{H_2SO_4} N_2F_4 + 2\ CO_2 + 2\ NH_4^+ + Cr^{3+}$$

Fluorourea, the intermediate in the synthesis of N, N-difluorourea, can be obtained when an equimolar amount of fluorine is used in the fluorination of urea.[11] Even under these conditions, the major product is N, N-difluorourea indicating that in aqueous solution fluorourea is fluorinated more rapidly than urea.

$$NH_2CONH_2 + F_2 \longrightarrow NHFCONH_2 \xrightarrow{F_2} NF_2CONH_2$$

The fluorine nmr spectrum of fluorourea consisting of a broad signal indicates that the NHF-hydrogen is highly labile.

Fluorourea, a white solid, mp 56-57°, is stable to prolonged storage at -20° but decomposes gradually at ambient temperature in a matter of several days. Its aqueous solution decomposes much faster to give azodicarbondiamide:

$$2\ NHFCONH_2 \longrightarrow NH_2CON = NCONH_2$$

A number of other reactions of fluorourea are described in the original article.[11]

Soon after the synthesis of N, N-difluorourea we initiated the investigation of fluorination of substituted ureas.[16] Banks, Hazeldine and Lalu[17] confirmed our findings regarding the fluorination of aqueous urea and extended aqueous fluorination reactions to several 1, 3-dialkylureas.[18] They found that fluorination of 1, 3-dimethylurea gave the N-monofluoro derivative and difluoroaminomethane; 1, 3-diethylurea yielded analogous products, and the fluorination of trimethylurea gave difluoraminomethane.

We examined the fluorination of mono-substituted ureas and cyclic ureas in greater detail.[11] The fluorination of simple alkylureas yielded the

corresponding difluoroaminoalkanes and N-alkyl-N', N'-difluoroureas according to the following general stepwise fluorination scheme:

$$\begin{array}{ccccc} RNHCONH_2 + F_2 & \longrightarrow & RNFCONH_2 & + & RNHCONHF \\ & & \downarrow F_2 & & \downarrow F_2 \\ & & RNF_2 + CO_2 + NH_4F & & RNHCONF_2 \end{array}$$

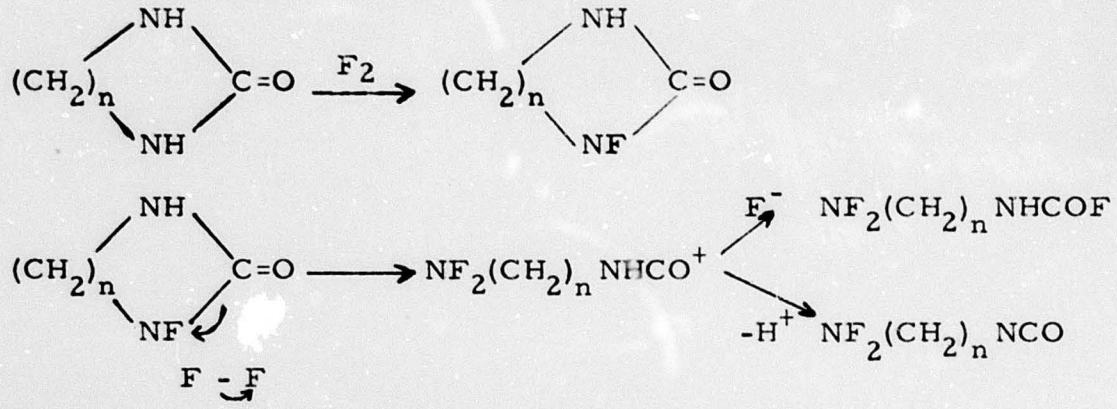
$$R = C_2H_5,\ \underline{n}\text{-}C_3H_7,\ \underline{c}\text{-}C_6H_{11},\ C_2H_5OCOCH_2^-$$

In some cases the N-fluoro derivatives could be isolated from underfluorinated mixtures. The failure to isolate N, N'-difluoroderivatives in these reactions indicates that, disregarding whether a hydrogen or an acyl group is displaced, the N-fluoro derivatives undergo fluorination on NF nitrogen more readily than on the NH nitrogen.

The fluorination of cyclic ureas, 2-imidazolidone and tetrahydropyrimidone, gave ω-(difluoroamino)alkylisocyanates and ω-(difluoramino)-alkylcarbamyl fluorides:

$$\begin{array}{c} NH \\ / \quad \backslash \\ (CH_2)_n \qquad C{=}O \\ \backslash \quad / \\ NH \end{array} + 2F_2 \longrightarrow NF_2(CH_2)_n NCO + NF_2(CH_2)_n NHCOF \qquad n = 2, 3$$

The formation of the carbamyl fluorides can be rationalized as the electrophilic displacement of acylium ions from the monofluoro intermediates. The resulting ions can react with fluoride to give the carbamyl fluorides or lose a proton to yield isocyanates:



C. Fluorination of Carbamates

With the objective of extending the scope of direct liquid phase fluorination reactions to different classes of nitrogenous compounds, in 1961 we began the study of fluorination of simple carbamic acid esters and N-alkyl-carbamates in aqueous and nonaqueous solutions. Meanwhile, Banks, Haszeldine and Lalo[17] in 1964 reported that the fluorination of aqueous urethane gave its N-fluoro derivative, and ethyl methylcarbamate gave methyldifluoramine. The preliminary results of our work were presented[19] in 1965 and a thorough discussion can be found in two recent papers[20,21] dealing with the subject.

Fluorination of simple alkyl carbamates in aqueous solution with one mole of fluorine gave alkyl N-fluorocarbamates in 25-30% yields. Attempts to increase this yield by employing more fluorine actually decreased the yield of the products, but difluoramine was detected in the exhaust gases. It became evident that the alkyl fluorocarbamates were fluorinated at a rate comparable to that of the fluorination of carbamates and that the resulting difluorocarbamates were rapidly hydrolyzed to difluoramine:

$$NH_2CO_2R + F_2 \xrightarrow{H_2O} NHFCO_2R \xrightarrow{F_2} [NF_2CO_2R] \longrightarrow HNF_2 + CO_2 + ROH$$

$R = CH_3,\ C_2H_5,\ \underline{i}\text{-}C_3H_7,\ \underline{n}\text{-}C_4H_9$

Subsequently, alkyl N, N-difluorocarbamates were synthesized by fluorinating alkyl carbamates with two moles of fluorine in nonaqueous solvents, such as methylene chloride, carbon tetrachloride, 1,1,2-trichloro-1,2,2-trifluoroethane, or acetonitrile:

$$NH_2CO_2R + 2F_2 \xrightarrow{CH_3CN} NF_2CO_2R + 2HF$$

Alkyl fluorocarbamates and difluorocarbamates were found to be useful intermediates in the synthesis of other NF compounds.[20] Thus, alkali salts of ethyl fluorocarbamate reacted with dimethyl sulfate, ethyl chloroformate, chlorine, and bromine to give, respectively, ethyl N-fluoro-N-methylcarbamate, diethyl fluoraminodicarboxylate, ethyl N-chloro-N-fluorocarbamate, and ethyl bromofluorocarbamate. Ethyl fluorocarbamate was added to a number of olefinic compounds.[20] Alkyl fluorocarbamates reacted with strong mineral acids to give fluoroammonium salts.[22]

$$NHFCO_2R + HX \xrightarrow[\Delta]{} NH_3F^+X^- + CO + RX$$

$R = C_2H_5,\ \underline{i}\text{-}C_3H_7$

$X = ClO_4^-,\ CH_3SO_3^-$

Alkyl difluorocarbamates reacted with water and alcohols to give difluoramine, and with sodium hypochlorite to give chlorodifluoramine:[20]

$$NF_2CO_2R + H_2O \longrightarrow HNF_2 + CO_2 + ROH$$

$$NF_2CO_2R + R'OH \longrightarrow HNF_2 + R'OCOR \quad (O)$$

$$NF_2CO_2R + NaOCl \longrightarrow ClNF_2$$

The hydrolysis-oxidation of alkyl difluorocarbamates with aqueous oxidizing agents such as, for example, chromic acid, gives tetrafluorohydrazine:[23]

$$2\ NF_2CO_2R + H_2O + Cr^{6+} \longrightarrow N_2F_4 + 2\ CO_2 + 2\ ROH + Cr^{3+}$$

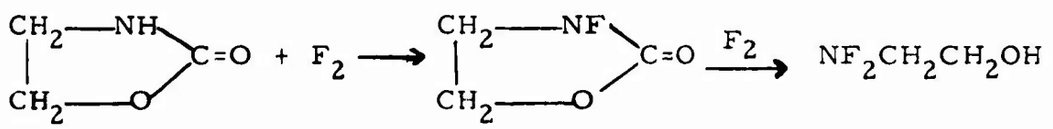
The fluorination of N-substituted carbamates yields the corresponding N-fluoro derivatives which react with another mole of fluorine to give difluoramino compounds:[21]

$$RNHCO_2R' + F_2 \longrightarrow RNFCO_2R' \xrightarrow{F_2} RNF_2$$

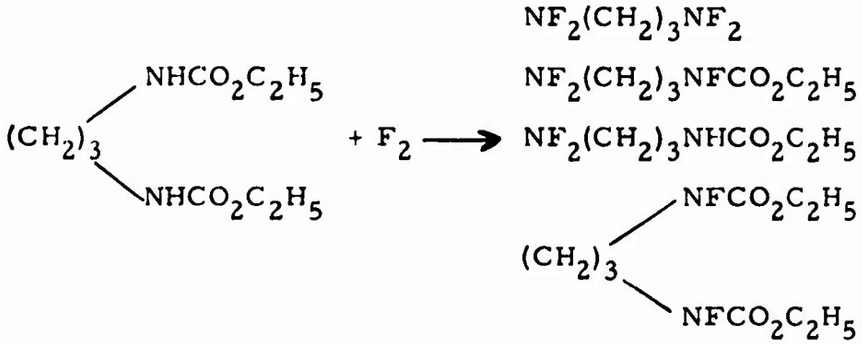
$$R = CH_3,\ \underline{n}\text{-}C_4H_9,\ \underline{sec}\text{-}C_4H_9,\ \underline{c}\text{-}C_5H_{11},\ \underline{c}\text{-}C_6H_{13},\ FC(NO_2)_2CH_2$$

These reactions represent successive fluorination of NH and fluorinalysis of carboalkoxy groups. As it was the case with the fluorination of unsubstituted carbamates, here, too, the rates of the two reactions are of the same order of magnitude and the N-fluoro derivatives cannot be obtained in high yields.

The fluorination of a cyclic carbamate, 2-oxazolidone, gave the N-fluoro derivative and 2-difluoraminoethanol:



The fluorination of several polyfunctional carbamates[21] was also investigated. Thus, the fluorination of the diethyl trimethylenecarbamate gave 1,3-bis(difluoramino)propane, ethyl 3-(difluoraminopropyl)fluorocarbamate, ethyl 3-(difluoraminopropyl)carbamate, and diethyl N,N'-difluorotrimethylene-dicarbamate:



The fluorination of diethyl ethylenedicarbamate and diethyl 3-nitraza-1,5-pentanedicarbamate yielded analogous products.

This method for the synthesis of difluoramino compounds has advantages of generality and simplicity compared with several other reported methods. The addition of difluoramine[14,24,25] to olefinic compounds does not yield simple primary derivatives, and reactions of tetrafluorohydrazine are limited in scope.[26-29] The fluorination of buffered aqueous amines in many cases gives impure products.[30]

D. Fluorination of Guanidine Derivatives

The synthesis of fluorinated guanidines has recently been described by several different groups of investigators.[31-36] We did limited work in this area by employing the technique of displacing carboalkoxy groups developed in

the fluorination of carbamates and using carboalkoxyguanidines, 1, 3-dicarboalkoxyguanidines and 1-carboethoxy-3-cyanoguanidine as the substrates. The fluorination of carboalkoxyguanidines in aqueous and acetonitrile solutions or suspensions with 4 moles of fluorine yielded mixtures of syn and anti isomers of the corresponding carboalkoxytetrafluoroguanidines in ca 10% yields:

$$NH_2C(=NH)NHCO_2R + 4F_2 \xrightarrow{(H_2O)} NF_2C(=NF)NFCO_2R + NFC(=FN)NFCO_2R$$

$$R = \underline{i}\text{-}C_3H_7,\ \underline{n}\text{-}C_4H_9$$

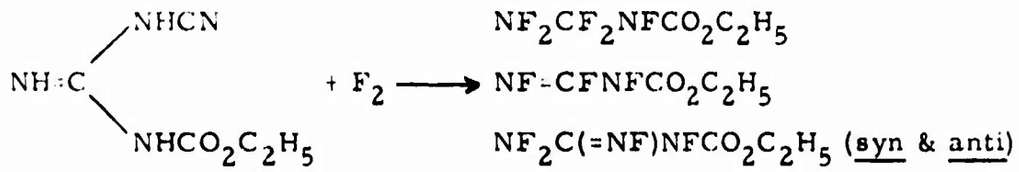
The syn and anti isomers were not separated. The configurations were assigned and relative amounts of the isomers were estimated on the basis of the fluorine nmr spectra.

The fluorination of 1, 3-dicarboalkoxyguanidines under similar conditions gave both dicarboalkoxytrifluoroguanidines and carboalkoxytetrafluoroguanidines:

$$NH{=}C(NHCO_2R)_2 + F_2 \longrightarrow FN{=}C(NFCO_2R)_2 \xrightarrow{F_2} FN{=}C(NF_2)(NFCO_2R)$$

$$R = C_2H_5,\ \underline{i}\text{-}C_3H_7$$

The fluorination of 1-carboethoxy-3-cyanoguanidine in acetonitrile with 6 moles of fluorine gave a mixture of products containing ethyl N-(difluoraminodifluoromethyl-N-fluorocarbamate, ethyl N-fluoraminofluoromethyl)-N-fluorocarbamate, and 1-carboethoxytetrafluoroguanidine at a 1:2:1 ratio:



E. Fluorination of Amides

Prior to our work the fluorination studies of amides were limited to acetamide and N-methylacetamide. The fluorination of aqueous acetamide was reported to give acetic acid, carbon dioxide, nitrous oxide and a trace of tetrafluorohydrazine, and that of N-methylacetamide yielded acetic acid, carbon dioxide and difluoraminomethane (7% yield).[17,18] We investigated the fluorination of a variety of secondary amides[37] using solutions or suspensions of the substrates in water or acetonitrile and found that these reactions are similar to those of carbamates proceeding by successive fluorination of NH and fluorinalysis of acyl groups to give N-fluoramides and difluoroaminoalkanes:

$$RNHCOR' + F_2 \longrightarrow RNFCOR' \xrightarrow{F_2} RNF_2$$

$R = CH_3,\ C_2H_5,\ \underline{n}\text{-}C_4H_9,\ HO_2CCH_2CH_2;\ R' = H,\ CH_3$

The rates of the two steps are of the same order of magnitude, as it was the case in the fluorination of ureas and carbamates, and these fluorination reactions are highly selective towards nitrogen. As a practical synthesis method for difluoraminoalkanes, amides in many instances are a more convenient source of starting materials.

N-Fluoro-N-aklylamides could be isolated in the above reactions and were found to be relatively stable towards hydrolysis. They hydrolyzed in concentrated sulfuric acid to give N-fluoroalkylammonium salts. Thus, methyl-N-fluoroformamide and ethyl-N-fluoroformamide yielded methylfluorammonium and ethylfluorammonium ion, respectively:[37]

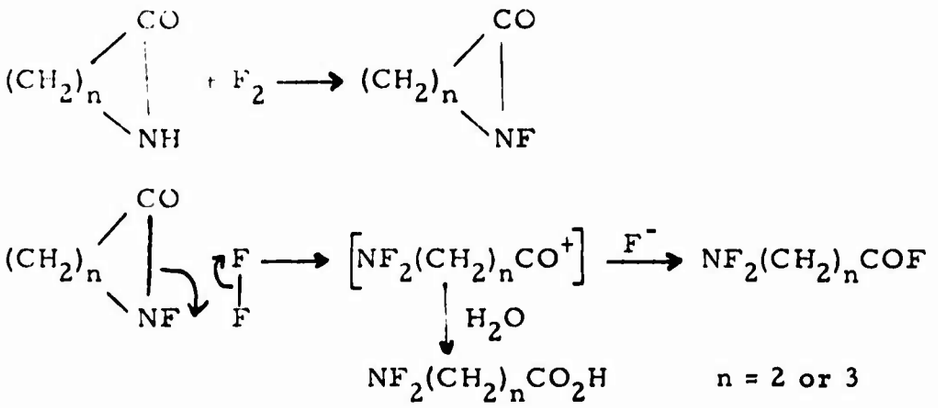
$$HCONFR + H_2SO_4 \longrightarrow RNH_2F^+ \; HSO_4^-$$
$$R = CH_3,\ C_2H_5$$

The fluorination of N, N'-diformyl-1, 3-diaminopropane, a difunctional amide, yielded 1, 3-bis(difluoramino)propane, N, N, N'-trifluoro-N'-formyl-1, 3-diaminopropane, and a very small amount of 1, 3-bis(difluoramino)-1-fluoropropane:

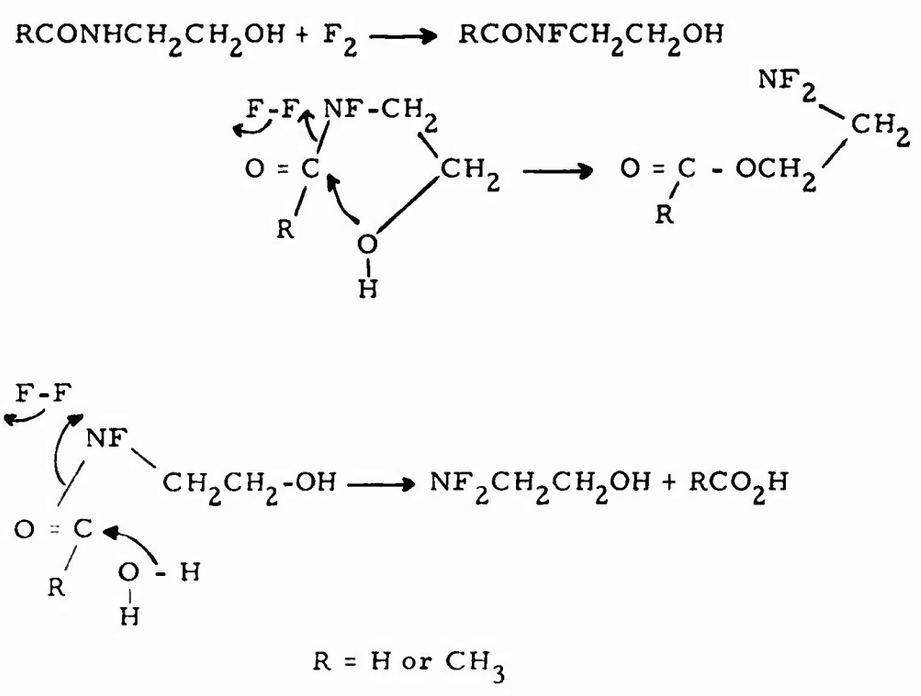
$$(CH_2)_3\begin{matrix}\diagup NHCHO \\ \diagdown NHCNO\end{matrix} + F_2 \longrightarrow NF_2(CH_2)_3NF_2 + NF_2(CH_2)_3NFCHO + NF_2(CH_2)CHFNF_2$$

The latter compound provides an example of CF fluorination also observed in other cases when excessive amounts of fluorine were employed.

The fluorinolysis of acyl groups in the fluorination of secondary amides can be rationalized as an electrophilic displacement of acylium ions by fluorine. In the case of lactams,[37] the acyl fragment is retained as a carboxy group or as acyl fluoride, respectively, depending if the fluorination is carried out under aqueous or nonaqueous conditions:



Evidence favoring this mechanism was found in the fluorination of N-acyl-ethanolamines.[37] The fluorination of the formyl and the acetyl derivatives with two moles of fluorine in aqueous solution gave 2-difluoraminoethanol and its corresponding esters, indicating that alkoxy groups are competing with water for acylium ions:



The fluorination of primary and tertiary amides was examined briefly. The fluorination of cyclohexanecarboxamide in acetonitrile with two moles of fluorine yielded a mixture of cyclohexyl isocyanate and cyclohexanecarboxylic acid. In a control experiment the starting material was not hydrolyzed by dilute aqueous hydrofluoric acid and it was concluded that the precursor of the carboxylic acid was difluoroamide which would be expected to be susceptible to hydrolysis.[38] The precursor of the isocynate most likely was the N-monofluoroamide which underwent Hofmann rearrangement:

$$RCONH_2 + F_2 \longrightarrow RCONHF \xrightarrow{HF} RNCO$$
$$\downarrow F_2$$
$$RCONF_2 \xrightarrow{H_2O} RCO_2H + HNF_2$$

Additional evidence for a difluoromaide intermediate was obtained in the fluorination of acetamide. The fluorination mixture in acetonitrile with two moles of fluorine was oxidized with aqueous chromic acid to give tetrafluorohydrazine.[37] This reaction, similar to that of preparation of tetrafluorohydrazine from difluorocarbamates.[23] indicates that either N, N-difluoroacetamide or its hydrolysis product, difluoramine, were present in the fluorination mixture.

The fluorination of aqueous formamide[15] yielded N, N-difluorourea suggesting that N-fluoroformamide intermediate underwent Hofmann rearrangement to give cyanic acid which in turn yielded urea.

The fluorination of undiluted dimethylformamide[15] yielded a colorless, strongly oxidizing solution stable at -20°. At higher temperatures,

or upon the addition of water, the fluorination mixture decomposed yielding methylamine as one of the products. It was assumed that the fluorination of dimethylformamide proceeded via fluorinolysis of the substrate to give dimethylfluoramine which at higher temperatures decomposed with the elimination of hydrogen fluoride:

$$HCON(CH_3)_2 + F_2 \longrightarrow [HCOF] + FN(CH_3)_2$$

$$FN(CH_3)_2 \xrightarrow{-HF} [CH_2 = NCH_3] \xrightarrow{H_2O} HCHO + CH_3NH_2$$

Dimethylfluoramine was synthesized by Wiesboeck and Ruff[39] in the fluorination of unsymmetrical dimethylsulfamide and the compound was found to be unstable at ambient temperatures.

Direct liquid phase fluorination of organic sulfur compounds explored by Wiesboeck and Ruff yield analogous difluoramino compounds as those obtained from ureas, carbamates and amides. In 1965 these investigators obtained N,N-difluorosulfamide[40] in the fluorination of aqueous sulfamide. The compound undergoes analogous reactions to those of N,N-difluorourea. More recently, Wiesboeck and Ruff[41] extended the scope of this reaction and reported high yields of simple difluoraminoalkanes in the fluorination of aqueous N-alkysulfamides, N-alkylsulfamates, and N-alkylsulfonamides.

IV. FLUORINATION OF AQUEOUS ALKALI SALTS OF ORGANIC ACIDS

Another application of the direct liquid phase fluorination technique was the fluorination of aqueous alkali salts of acidic organic compounds proceeding by the following schematic equation:

$$R^- Na^+ + F_2 \xrightarrow{(H_2O)} RF + NaF$$

This category of substrates includes nitronate salts, salts of primary nitramines, and carboxylic acid salts.

A. Fluorination of Nitronate Salts

In 1960 we became involved in the synthesis of aliphatic fluoronitro compounds and learned that there were no general methods for the synthesis of α-fluoronitroalkanes. The direct chlorination and bromination of nitronate salts was known,[42] but only indirect methods were employed for fluorination. The fluorination with perchloryl fluoride[43,44] and perfluoropiperidine[45] is limited in scope and more general and simpler techniques were desirable. Being in the midst of the study of direct fluorination of nitrogenous compounds, we applied this technique to nitroalkanes and found that direct fluorination of aqueous solutions of nitronate salts yielded the corresponding α-fluoro derivatives.[46,47] Salts of terminal gem-dinitro compounds and nitroform gave the corresponding fluoronitroalkanes in 80-95% yields:

$$RC(NO_2)_2^- Na^+ + F_2 \xrightarrow{H_2O} RC(NO_2)_2F + NaF$$

$$R = CH_3,\ C_2H_5,\ HOCH_2,\ \text{and}\ NO_2$$

2-Fluoro-2,2-dinitroethanol readily available in this reaction became an important intermediate in the aliphatic fluoronitro chemistry.[48,49]

Numerous publications on the synthesis and reactions of aliphatic fluoronitro compounds began to appear in 1968. A review on aliphatic fluoronitrocarbons by Bissell[50] illustrates mushrooming of publications in this area

of research. This review, covering the literature to 1968, contains only three references to direct liquid phase fluorination of nitronate salts. Since then some 100 papers dealing with the subject appeared, and some of the more pertinent publications are listed in References 51-59. The work by Eremenko and his co-workers in USSR is by far the most voluminous. Recently, Eremenko and Nesterenko reported the synthesis of a number of fluoronitrocarbons by direct liquid phase fluorination of nitroalkyl mercurials.[60-62]

The aqueous fluorination technique was found to be less satisfactory in the fluorination of alkali salts of simple mononitroalkanes.[47] The sodium salts of nitroethane and 1-nitropropane gave 1-fluoro-1-nitroethane and 1-fluoro-1-nitropropane in ca 10% yields:

$$RCHNO_2^- Na^+ + F_2 \longrightarrow RCHFNO_2 + NaF$$

$$R = CH_3,\ C_2H_5$$

Large amounts of starting materials were recovered in these reactions. The competing fluorination of hydroxide ions seems to be responsible for the low yield of fluoronitroalkanes.

The direct liquid phase fluorination of salts of mononitro compounds has been used to synthesize α-fluoronitro-substituted malonates,[63] cyanoacetates,[63] ketones,[64] nitriles,[64] and alcohols.[65-67] The fluorination of aqueous nitronate salt of ethyl 2-nitropentanoate gave ethyl 2-fluoro-2-nitropentanoate in 85% yield demonstrating the activating effect of a carboalkoxy group.[66]

The fluorination of nitroalkanes[15] was found to be very sluggish as compared with that of aqueous nitronate salts. Fluorine was very poorly consumed in the fluorination of 1-nitropropane in 1,1,2-trichloro-1,2,2-trifluoroethane solution at ambient temperature. The major product of this reaction was 3-fluoro-1-nitropropane. Small amounts of 2-fluoro-1-nitropropane and 3,3-difluoro-1-nitropropane were also identified. Under similar fluorination conditions, 1,1-dinotroethane evolved nitrogen oxides yielding some 1,2-difluoro-1-nitroethane among a number of other products.

The oxidation of 3-nitro-2-butanol by elemental fluorine was recently reported by Fokin, et al.[68]

B. Fluorination of Primary Nitramines

The fluorination of primary aliphatic nitramines[69] under the conditions employed in the fluorination of nitroalkane appeared feasible. Primary nitramines are acidic and readily form alkali salts in aqueous solutions. N-Chloro derivatives of primary nitramines are well known.

The fluorination of aqueous alkali salts of simple aliphatic primary nitramines at 0-5° gave the corresponding N-fluoro derivatives in good yields:[70]

$$RNNO_2^- Na^+ + F_2 \xrightarrow{H_2O} RNFNO_2 + NaF$$

Physical properties of N-fluoro-N-nitrobutylamine isomers[71,72] were explored to some extent, but otherwise little work has been done in this area. Subsequently, we found that N-fluoro-N-nitroamines can also be synthesized in the nitration of alkyl N-alkyl-N-fluorocarbamates:[73]

$$RNFCO_2R' + HNO_3 \longrightarrow RNFNO_2 + CO_2 + R'ONO_2$$

C. Fluorination of Carboxylic Acid Salts

Attempts to extend the scope of direct liquid phase fluorination technique to yet different classes of organic compounds led to the investigation of direct fluorination of aqueous alkali salts of carboxylic acids.[74] Bockemuller[3] reported β- and γ-substitution in the liquid phase fluorination of butyric acid and also reported that acetic, succinic, and glutaric anhyhydrides and acetic acid were inert towards fluorine in dilute carbon tetrachloride solution. Fichter and Brunner[4] obtained methanol, formaldehyde, carbon dioxide, and ethylene in the fluorination of aqueous potassium acetate, and ethanol, acetaldehyde and ethylene in the fluorination of propionate.

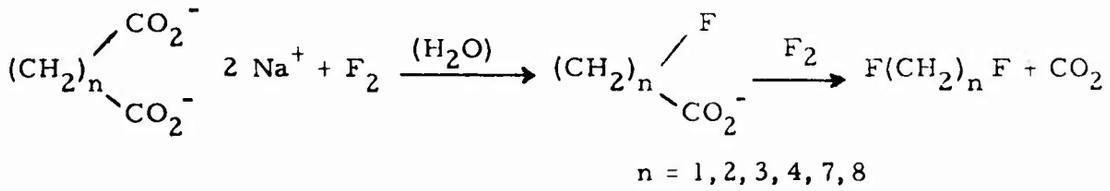
We investigated direct fluorination of aqueous alkali salts of several aliphatic monocarboxylic at 0-5° and found that such reactions proceed by decarboxylation to give 1-fluoroalkanes:

$$RCO_2^- Na^+ + F_2 \longrightarrow RF + CO_2 + NaF$$

1-Fluoroalkanes, the primary products of these reactions, underwent some random fluorination, making the identification of reaction products difficult. Thus, the fluorination of sodium nonanoate and sodium decanoate yielded impure 1-fluorooctane and 1-fluorononane, respectively.[74] The fluorination of aqueous sodium methyl adipate with one mole of fluorine gave methyl 5-fluoropentanoate in 14% yield:

$$CH_3O_2C(CH_2)_4CO_2^- Na^+ + F_2 \xrightarrow{H_2O} CH_3O_2C(CH_2)_4F + CO_2 + NaF$$

The fluorination of aqueous alkali salts of dicarboxylic acids[74] proceeded stepwise yielding ω-fluorocarboxylic acids and α,ω-difluoroalkanes:



n = 1, 2, 3, 4, 7, 8

α,ω-Difluoroalkanes underwent some random fluorination. The recovered starting materials and ω-fluorocarboxylic acids, the monofluorination products, were not randomly fluorinated. α,ω-Difluoroalkanes apparently solubilize fluorine better than the water and higher concentration in the organic phase provides favorable conditions for random fluorination. The fact that little, if any, random fluorination took place in the aqueous phase indicates that fluorine reacts at a much faster rate with carboxylate anion than with the hydrocarbon backbone. The preparative value of these fluorinations would be strengthened if the random fluorination of primary reaction products could be suppressed or eliminated.

The fluorination of aromatic carboxylic acids was investigated only briefly. At about the same time we were studying the fluorination of aromatic compounds and it became apparent that fluorination in aromatic nuclei would interfere with the decarboxylative fluorination of aromatic carboxylic acids. Although this conclusion is generally true and, for example, no products could be isolated in the fluorination of aqueous sodium benzoate, it appeared that with electronegatively substituted aromatic carboxylic acids the decarboxylative

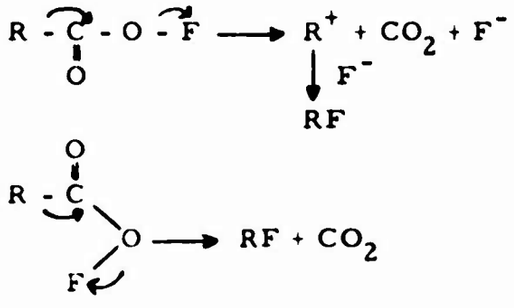
fluorination might compete with the fluorination in the aromatic nucleus. This was found to be the case and fluorination of aqueous sodium p-nitrobenzoate[74] gave p-fluoronitrobenzene in 4% yield:

$$\text{p-}NO_2C_6H_4CO_2^- Na^+ + F_2 \xrightarrow{H_2O} \text{p-}NO_2C_6H_4F + CO_2 + NaF$$

Aqueous fluorination of alkali carboxylates can be looked upon as a special case of the Hunsdieker reaction proceeding via acyl hypofluorite intermediates.[74] Whereas only indirect evidence exists for acyl hypobromites, several perfluoroacyl hypofluorites have been isolated,[75] and it was shown[76, 77] that they decompose into perfluoroalkanes and carbon dioxide. Acyl hypofluorites might very well be the intermediates in the fluorination of aqueous alkali carboxylates:

$$RCO_2^- Na^+ + F_2 \xrightarrow{(H_2O)} RCO_2F + NaF$$

The decomposition of these intermediates by a solvent-cage or SNi mechanism would account for the observed products:



V. FLUORINATION OF HYDROCARBONS

A. Introduction

Direct liquid phase fluorination of hydrocarbons has been the subject of only sporadic research efforts, and only a handful of publications deal with this subject. Books and review articles on fluorine chemistry need to devote but a few pages to review the work on direct liquid-phase fluorination.

In the fluorination of nitrogenous compounds and aqueous alkali salts of organic compounds, we did not encounter any problems with burning, charring and explosions so often reported in connection with direct fluorination reactions. This encouraged us to investigate the fluorination of hydrocarbons. With a few exceptions, our work was concerned primarily with the fluorination of aromatic compounds.

B. Fluorination of Methyl Trichloroacetate and Acetic Anhydride

Simple alkyl esters were considered to be sufficiently inert to fluorine to be used as the heat transfer media in the fluorination of nitrogenous compounds. It was found, however, that acetates and formates react readily with fluorine. This observation led to the investigation of direct fluorination of several esters.[78]

The fluorination of ethyl acetate in 1,1,2-trichloro-1,2,2-trifluoroethane solution with one mole of fluorine gave a mixture of products containing fluorine in both acid and alcohol portions of the molecule and it became apparent that simpler substrates were needed in order to simplify the characterization of products. Consequently, methyl trichloroacetate,

containing the "blocked" acid portion of the molecule, was fluorinated with one mole of fluorine, and the major reaction product was characterized as fluoromethyl trichloroacetate:

$$CCl_3CO_2CH_3 + F_2 \longrightarrow CCl_3CO_2CH_2F + HF$$

Fluoromethyl trichloroacetate underwent further fluorination to give difluoromethyl trichloroacetate:

$$CCl_3CO_2CH_2F + F_2 \longrightarrow CCl_3CO_2CHF_2 + HF$$

No concerted efforts were made to synthesize trifluoromethyl trichloroacetate, yet another potential product in this fluorination.

Fluoromethyl esters have not been previously reported, and their nmr spectra might be of some general interest. The proton nmr spectrum of fluoromethyl trichloroacetate consisted of a doublet at $\delta 5.89$, $J_{HF} = 50$ Hz, and its fluorine spectrum exhibited a triplet at $\phi 159.6$, $J_{HF} = 49.0$ Hz. The proton nmr spectrum of difluoromethyl trichloroacetate consisted of a triplet at $\delta 7.19$, $J_{HF} = 71.0$ Hz, and its fluorine spectrum of a doublet at $\phi 91.8$, $J_{HF} = 69.5$ Hz.

The fluorination of acetic anhydride, another model compound, with three moles of fluorine, followed by hydrolysis of the fluoroacetic anhydrides, gave a mixture of fluoroacetic acid and difluoroacetic acid:

$$(CH_3CO)_2O + F_2 \longrightarrow \text{fluoroacetic anhydrides} \xrightarrow{H_2O} FCH_2CO_2H + F_2CHCO_2H$$

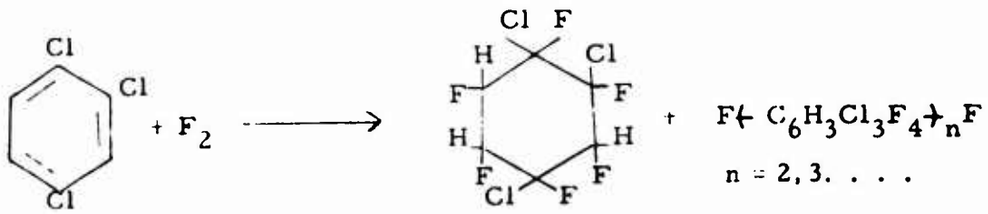
C. Fluorination of Aromatic Compounds

Early attempts to directly fluorinate aromatic compounds[79] resulted in explosions and the framentation of aromatic rings. Bancroft and Jones[80] in 1929 reported explosions using benzene or toluene. These reactions were moderated using fluorine diluted with nitrogen, but only tarry, noncharacterizable products were obtained.[81] Bockemuller[3] obtained tarry products in the fluorination of several simple aromatic compounds and concluded that under direct liquid phase fluorination conditions aromatic compounds undergo addition and polymerization rather than substitution reactions. More recently, Brooke, et al,[82] reported that fluorination of hexachlorobenzene gives an adduct with the average composition $C_6F_6Cl_6$.

The experience of the above researchers implied that fluorination of benzene and monosubstituted benzenes might indeed be uncontrollable. On the other hand, the successful fluorination of hexachlorobenzene suggested that other highly halogenated aromatic compounds might also add fluorine. Consequently, a number of such substrates were examined under direct liquid phase fluorination conditions.[83,84]

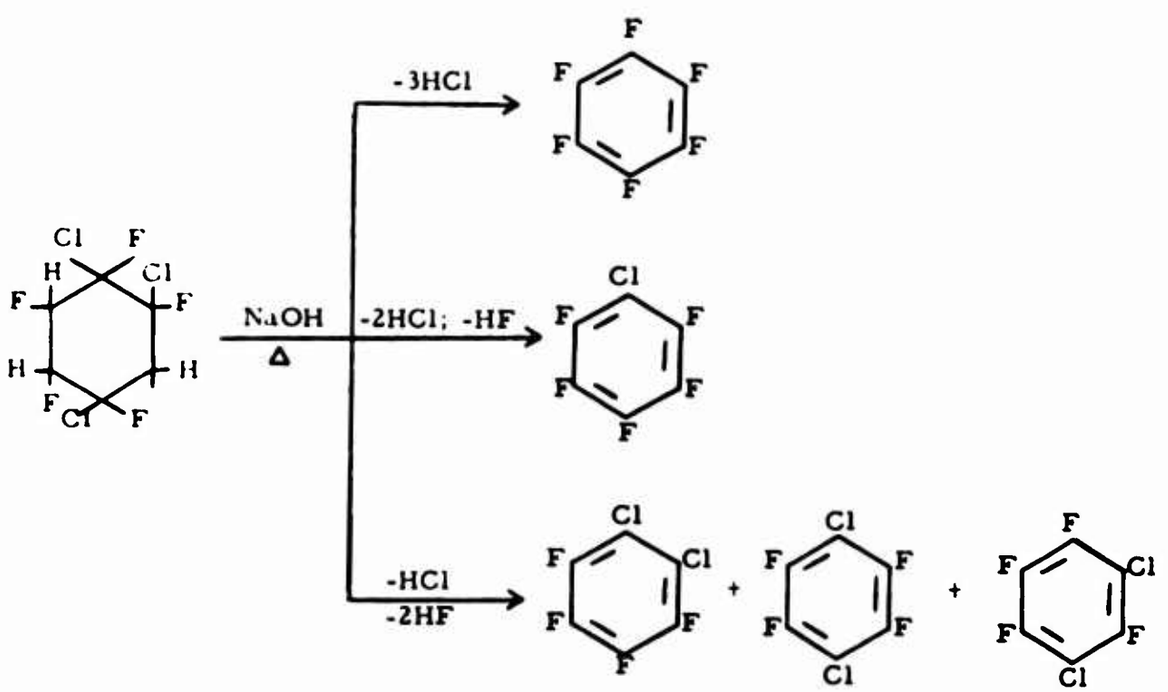
1,2,4-Trichlorobenzene and 1,3,5-trichlorobenzene underwent smooth fluorination in 1,1,2-trichloro-1,2,2-trifluoroethane solution at $0 \pm 5^{\circ}$ consuming three moles of fluorine. In both cases the weights of reaction products amounted to the sum of weights of fluorine and trichlorobenzene indicating that these fluorinations proceeded by addition rather than by substitution.

The crude reaction product of the fluorination of 1, 2, 4-trichlorobenzene was fractionated to give 1, 2, 3, 4, 5, 6-hexafluoro-1, 2, 4-trichlorocyclohexane, hexachlorodecafluorobicyclohexyl, and polytrichlorotetrafluorocyclohexene in a 5:3:2 ratio, respectively:



Similarly, the fluorination products of 1, 3, 5-trichlorobenzene were characterized as 1, 2, 3, 4, 5, 6-hexafluoro-1, 3, 5-trichlorocyclohexane, decafluorohexafluorobicyclohexyl, and polytrichlorotetrafluorocyclohexene.

1, 2, 3, 4, 5, 6-Hexafluoro-1, 2, 4-trichlorocyclohexane underwent a facile dehydrohalogenation when treated with sodium hydroxide to give a mixture of hexafluorobenzene, chloropentafluorobenzene, and the three isomers of dichlorotetrafluorobenzene:



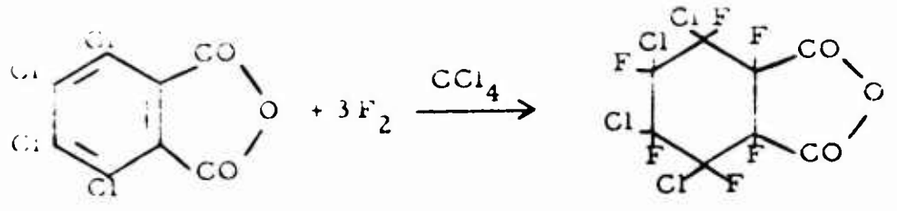
Under similar conditions, 1, 2, 3, 4, 5, 6-hexafluoro-1, 3, 5-trichlorocyclohexane underwent dehydrohalogenation and gave a mixture of aromatic compounds similar in composition to that obtained from the 1, 2, 4-trichloro isomer. m-Dichlorotetrafluorobenzene was the only dichlorotetrafluorobenzene isomer in this dehydrohalogenation.

Decafluorobiphenyl was identified as one of the products in dehydrohalogenation of decafluorohexachlorobicyclohexyls, the dimeric fluorination products of 1, 2, 4-trichlorobenzene and 1, 3, 5-trichlorobenzene, with aqueous sodium hydroxide at 80-100°.

o-Dichlorobenzene underwent fluorination in 1, 1, 2-trichloro-1, 2, 2-trifluoroethane solution and consumed approximately three moles of fluorine. The distillable portion of the fluorination product analyzing for $C_6H_4Cl_2F_6$ was characterized as 1, 2-dichloro-1, 2, 3, 4, 5, 6-hexafluorocyclohexane. The distillation residue, analyzing for $C_{12}H_8Cl_4F_{10}$, molecular weight 575 ± 60, was characterized as decafluorotetrachlorobicyclohexyl. The fluorination of p-dichlorobenzene proceeded similarly, yielding a mixture of 1, 4-dichloro-1, 2, 3, 4, 5, 6-hexafluorocyclohexane, decafluorotetrachlorobicyclohexyl, and polydichlorotetrafluorocyclohexenes.

1, 2, 4, 5-Tetrachlorobenzene was fluorinated in carbon tetrachloride to give 1, 2, 3, 4, 5, 6-hexafluoro-1, 2, 4, 5-tetrachlorocyclohexane and polytetrafluorotetrachlorocyclohexene.

The fluorination of tetrachlorophthalic anhydride in carbon tetrachloride yielded hexafluoro-3, 4, 5, 6-tetrachlorocyclohexane-1, 2-dicarboxylic acid anhydride and no polymeric products:



The fluorination of several halogenated biphenyls was also investigated. Tetrachlorobiphenyl[85] gave a product analyzing for $C_{12}H_6Cl_4F_{10}$, molecular weight 750 ± 75. The material was separated into two fractions: the distillate, characterized as dodecafluorotetrachlorobicyclohexyl, and the distillation residue consisting of a mixture of fluorinated dimers and higher molecular weight condensation products of the general empirical structure $(C_{12}H_6Cl_4F_{10})_n$.

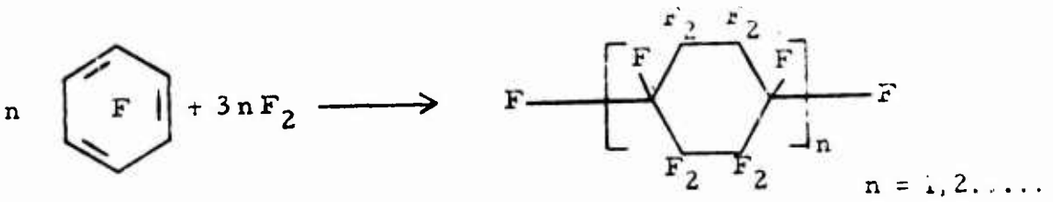
$$C_6H_3Cl_2 - C_6H_3Cl_3 + F_2 \longrightarrow F\left[C_6H_3F_5Cl_2 - C_6H_3F_5Cl_2\right]_nF$$

The fluorination of hexachlorobiphenyl[85] gave a mixture of the dodecafluoro adduct and higher molecular weight polydecafluorohexachlorobicyclohexenes.

$$C_6H_2Cl_3 - C_6H_2Cl_3 + F_2 \longrightarrow F\left[C_6H_2Cl_3F_5 - C_6H_2Cl_3F_5\right]_nF$$
$$n = 1, 2, 3. \ldots .$$

The facile fluorination of chlorinated aromatic compounds suggested that fluorinated benzenes might also undergo fluorination. Consequently, hexafluorobenzene was fluorinated in 1,1,2-trichloro-1,2,2-trifluoroethane at 20° with 3 moles of fluorine. The product was distilled to give perfluorobicyclohexyl and several fractions of higher molecular weight products identified as polydecafluorocyclohexenes. The yield of polyperfluorocyclohexenes amounted

to 55%, and, since all hexafluorobenzene was consumed, it was assumed that perfluorocyclohexane comprised the remainder of the product:



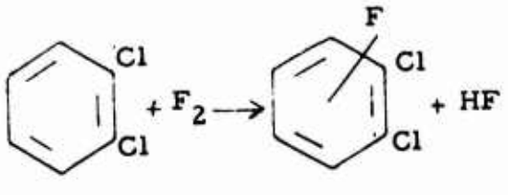
The mode of ring-to-ring junction of decafluorocyclohexyl units in the polymeric products has not been established, and some residual unsaturation, if present, would not have been detected by the elemental analyses.

The direct fluorination of hexafluorobenzene differed from that of hexachlorobenzene. Whereas in the latter case, the monomeric hexafluoro adduct was the sole reaction product, the fluorination of hexafluorobenzene yielded predominantly polymeric products. The polymerization in this case was more pronounced than in the fluorination of trichlorobenzenes or dichlorobenzenes.

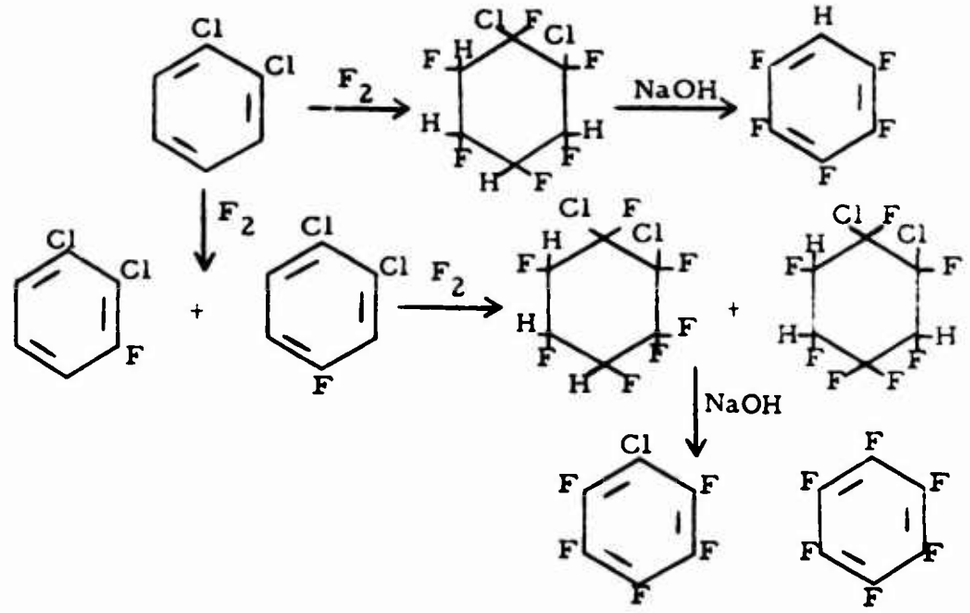
The fluorination of chloropentafluorobenzene proceeded similarly to that of hexafluorobenzene yielding polychlorononafluorocyclohexenes.

The fluorination of halogenated aromatic compounds proceeded smoothly even at fast fluorination rates except that of hexafluorobenzene, which in two cases ended in explosions occurring in the middle of fluorination runs. These explosions might have been caused by a sudden polymerization of octafluorocyclohexadiene intermediate.

Some unexpected results obtained in the dehydrohalogenation of 1,2-dichloro-1,2,3,4,5,6-hexafluorocyclohexane, the fluorination product of o-dichlorobenzene, led to the investigation of fluorine substitution in the aromatic nucleus. The product mixture of this dehydrohalogenation reaction contained hexafluorobenzene and chloropentafluorobenzene in addition to the expected pentafluorobenzene. The two former compounds must have resulted in the dehydrohalogenation of dichloroheptafluorocyclohexane, which in turn must have been produced in the displacement of hydrogen either before or after the addition. If the latter was the case, o-dichlorofluorobenzene must have been produced in the substitution fluorination of o-dichlorobenzene:

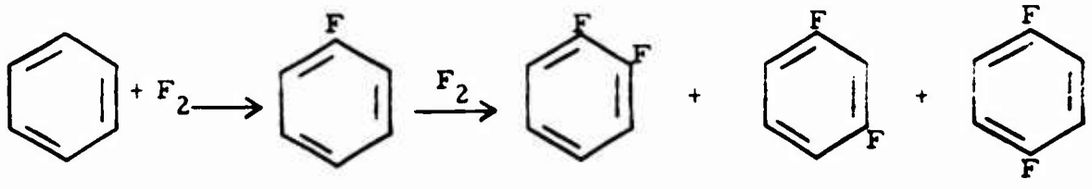


The possibility that o-dichlorobenzene underwent aromatic substitution prior to the addition was confirmed in the fluorination of the substrate at a low fluorine to substrate ratio. The results of this experiment confirmed the preceding considerations regarding the dehydrohalogenation reactions, and provided the first example of substitution in an aromatic nucleus under direct liquid phase fluorination conditions.[86] The fluorination of o-dichlorobenzene and dehydrohalogenation of monomeric products is represented as follows:



The aromatic substitution observed in the fluorination of o-dichlorobenzene led to the investigation of direct fluorination of a number of representative aromatic compounds[84] in order to assess the scope and the limitations of these reactions.

The fluorination of a dilute solution of benzene in acetonitrile at -35° with 0.7 mole of fluorine yielded predominantly the substitution products containing fluorobenzene, and the three isomers of difluorobenzene:

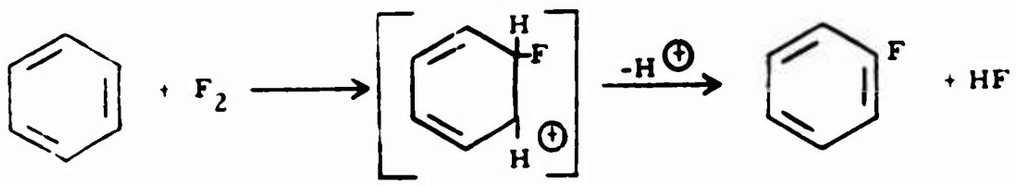


The approximate relative ratio of the products in the mixture was 1:4:5:60 for m-, o-, and p-difluorobenzene and fluorobenzene, respectively.

When the fluorination of benzene was conducted at higher molar ratios of fluorine to substrate, small amounts of aromatic fluorine compounds and large amounts of polymeric products were obtained. Thus, the fluorination of 7.8 g (0.1 mole) of benzene with 0.4 mole of fluorine yielded 13 g of viscous oil containing 63% fluorine. The fluorine nmr spectrum (broad envelope at ϕ 180-220) its approximate empirical structure, $C_6H_4F_6$, and its physical properties indicated that this material was a mixture of highly fluorinated polycyclohexenes. This data indicated that two consecutive reactions were operative in the fluorination of benzene: substitution, and addition-polymerization.

The relative ratio of the three difluorobenzene isomers obtained in the fluorination of benzene at a low fluorine to substrate ratio suggested that the direct liquid phase fluorination of aromatic compounds proceeds via electrophilic substitution analogous to the ionic halogenation reactions of aromatic compounds.[87] Evidence in support of this probable mechanism was obtained in the fluorination of o-p directing toluene, and m-directing nitrobenzene.

The fluorination of undiluted toluene at -70° yielded a mixture of ortho, meta, and para fluorotoluene isomers in a 1:5:4 ratio. The fluorination of nitrobenzene gave p-, m- and o-nitrobenzene in a 1:9:1.5 ratio. The ratio of ortho, meta, and para isomers observed in the fluorination of benzene, toluene and nitrobenzene indicated that direct liquid-phase fluorination of aromatic compounds proceeds by ionic electrophilic substitution:



The classical electrophilic substitution orientation rules observed in the fluoroination of these three substrates and other representative aromatic compounds are in support of this mechanism.

The fluorination of several other substituted benzenes and naphthalene proceeded in an analogous manner. The fluorination of 2,4-dinitrotoluene was sluggish and gave 2,4-dinitro-6-flurotoluene in a 5% yield. The deactivating effect of the two electronegative nitro groups on the nucleus was apparent. The bromination of 2,4-dinitrotoluene to the 6-bromo derivative requires concentrated sulfuric acid and a silver sulfate catalyst.[88]

The fluorination of naphthalene at low fluorine to substrate ratios yielded a mixture of α-fluoronaphthalene and β-fluoronaphthalene in a 3:1 ratio; only polymeric products containing 60-65% fluorine were obtained under exhaustive fluorination conditions. The low-temperature chlorination or bromination of naphthalene yields α-halo derivatives,[89,90] but β-bromonaphthalene is obtained at high temperatures.[90] Under the conditions of free-radical bromination[90] naphthalene undergoes addition.[91]

In almost all cases, the fluorine nmr spectra of fluorination mixtures of monosubstituted benzenes exhibited signals in the aromatic region other than those assigned to the o-, m-, and p-fluoro derivatives, indicating that aromatic polyfluoro derivatives were also produced in these reactions. Such polysubstituted compounds, however, could not be identified because of a great number of possible isomers. Attempts to increase the relative concentration of polyfluoro derivatives at higher fluorine to substrate ratios produced larger amounts of nonaromatic products. Thus, fluorination of

chlorobenzene at a low fluorine to substrate ratio yielded a mixture of o-, m-, and p-chlorofluorobenzenes, but a nonaromatic material analyzing for $C_6H_5ClF_4$ was obtained at a 3:1 ratio. The physical properties, bp >180° (0.1 mm), mp 127-128°and analytical data indicated that the material was a mixture of polychlorofluorocyclohexenes of an approximate composition $(C_6H_5ClF_4)_n$. In conjunction with the attempted identification of polysubstitution products, it became apparent that an aromatic substrate and its substitution products are consumed in addition and polymerization reactions at approximately the same rate as the fluorination progresses, and, that when a certain degree of substitution is reached, further fluorination proceeds predominantly by addition. Under exhaustive fluorination conditions, all substitution products are eventually consumed in addition actions.

It is important to note that in the fluorination of olefinic[92,93] and acetylenic[94] compounds containing aromatic substituents, Merritt did not observe any fluorination in the aromatic nucleus. Thus, with phenyl acetylene, diphenyl acetylene, and methyl phenyl acetylene, he obtained the corresponding tetrafluoroethane derivatives with no addition or substitution in the aryl groups. On the other hand, we found[15] that in the fluorination of styrene, even at fluorine to substrate ratios lower than one, the phenyl group underwent addition and substitution ractions at rates comparable to that of the addition to the olefinic bond. A comparison of the experimental conditions suggests that this apparent inconsistency between Merritt's work and ours might be the result of the difference in reaction temperatures. Merritt conducted his fluorinations at -78°, whereas we

fluorinated styrene at $0 \pm 5^{\circ}$. It is possible that rates of addition and substitution reactions in the fluorination of an aromatic compound might be also highly dependent on the fluorination temperature. This possibility was not examined, but if the above considerations are correct, our data on direct fluorination of aromatic compounds would represent only an arbitrary cross section, since practically all our fluorination experiments were conducted at $0 \pm 10^{\circ}$.

Our work on direct liquid phase fluorination of aromatic compounds was concerned with the feasibility of controllable direct liquid phase fluorination of aromatic compounds leading to defined products, which was found to be the case. Many important and interesting aspects of this broad area of research were beyond the scope of the screening-type study and remain to be investigated.

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MANNICH REACTIONS OF 2-Fluoro-2, 2-dinitroethanol

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ABSTRACT

2-Fluoro-2, 2-dinitroethanol undergoes the Mannich reaction with primary and secondary amines to give the corresponding 2-fluoro-2, 2-dinitroethylamines. In one example (allylamine), forcing conditions were used to obtain the corresponding bis-(2-fluoro-2, 2-dinitroethyl)amine. Hydrazine gave N, N' -bis-(2-fluoro-2, 2-dinitroethyl)hydrazine. Ammonia gave 2-fluoro-2, 2-dinitroethylamine which reacted with chloroformates to give N-fluorodinitroethyl carbamates.

β,β-Dinitroalcohols undergo the Mannich reaction with a variety of amines to give β,β-dinitroalkyl amines.[2] Published examples of the Mannich reaction of 2-fluoro-2,2-dinitroethanol are limited to ammonia[3,4] and to $NH_2C(CH_2OAc)_3$.[5] Ammonia yielded 2-fluoro-2,2-dinitroethylamine[3] or bis(2-fluoro-2,2-dinitroethyl)amine,[3,4] depending on the reaction conditions, whereas $NH_2C(CH_2OAc)_3$ gave the 1:1 condensation product. The present study explores the scope of the Mannich reaction of 2-fluoro-2,2-dinitroethanol.

The reactions of a variety of primary and secondary amines with 2-fluoro-2,2-dinitroethanol are summarized in Table 1. In aqueous solution at low temperatures, high yields of 1:1 condensation products were formed, and other functional groups, such as carboxy, acetal, hydroxy groups, did not interfere. The condensation also takes place in organic solvents; allylamine gave a 93% yield of N-(2-fluoro-2,2-dinitroethyl)allylamine when methylene chloride was used as the solvent.

More forcing conditions yielded the 2:1 condensation product of allylamine. Thus, when a neat mixture of 2-fluoro-2,2-dinitroethanol and the 1:1 condensation product, N-(2-fluoro-2,2-dinitroethyl)allylamine, was heated for 6 hrs at 90-95°, a 49% yield of N,N-bis(2-fluoro-2,2-dinitroethyl)-allylamine was isolated.

An attempt was also made to prepare a 2:1 product of glycine ethyl ester under forcing conditions (115-120°). The product, however, was identified as N,N'-bis(2-fluoro-2,2-dinitroethyl)-N,N'-bis(carbethoxymethyl)-methylenediamine. Formaldehyde, liberated by the decomposition of

TABLE 1

Reaction of 2-Fluoro-2, 2-dinitroethanol with Amines

Starting Material	Product	Yield %
CH_3NH_2	$CH_3NHCH_2CF(NO_2)_2$	72
$(CH_3)_2NH$	$(CH_3)_2NCH_2CF(NO_2)_2$	78
$HO_2CCH_2NH_2$	$HO_2CCH_2NHCH_2CF(NO_2)_2$	64
$C_2H_5O_2CCH_2NH_2$	$C_2H_5O_2CCH_2NHCH_2CF(NO_2)_2$	97
$(C_2H_5O)_2CHCH_2NH_2$	$(C_2H_5O)_2CHCH_2NHCH_2CF(NO_2)_2$	94
$HO_2CCH_2CH(CO_2H)NH_2$	$HO_2CCH_2CH(CO_2H)NHCH_2CF(NO_2)_2$	78
$HOCH_2CH_2NH_2$	$HOCH_2CH_2NHCH_2CF(NO_2)_2$	74
$CH_2=CHCH_2NH_2$	$CH_2=CHCH_2NHCH_2CF(NO_2)_2$	75 - 93
$CH_2=CHCH_2NHCH_2CF(NO_2)_2$	$CH_2=CHCH_2N\left[CH_2CF(NO_2)_2\right]_2$	49

2-fluoro-2, 2-dinitroethanol, apparently condenses with the active methylene group of the 1:1 adduct as follows:

$$C_2H_5O_2CCH_2NHCH_2CF(NO_2)_2 + CH_2O \longrightarrow$$

$$\begin{array}{l} C_2H_5O_2C\underset{\displaystyle CH_2OH}{\underset{|}{C}}HNHCH_2CF(NO_2)_2 \longrightarrow \end{array}$$

$$\begin{array}{l} C_2H_5O_2CCHNHCH_2CF(NO_2)_2 \\ \qquad\quad | \\ \qquad\quad CH_2 \\ \qquad\quad | \\ C_2H_5O_2CCHNHCH_2CF(NO_2)_2 \end{array}$$

The Mannich reaction of 2, 2-dinitropropanol with hydrazine has been reported to give N, N'-bis-(2, 2-dinitropropyl)hydrazine.[6] The corresponding reaction was found to take place with 2-fluoro-2, 2-dinitroethanol and hydrazine, to give N, N'-bis-(2-fluoro-2, 2-dinitroethyl)hydrazine.

$$FC(NO_2)_2CH_2OH + N_2H_4 \longrightarrow FC(NO_2)_2CH_2NHNHCH_2CF(NO_2)_2$$

We have previously reported the fluorination of methyl (2-fluoro-2, 2-dinitroethyl)carbamate to give methyl N-fluoro-N-(2-fluoro-2, 2-dinitroethyl)carbamate.[7] This starting material was synthesized by an _in situ_ acylation of 2-fluoro-2, 2-dinitroethylamine. The addition of methyl chloroformate to the crude solution formed by adding ammonia to aqueous 2-fluoro-2, 2-dinitroethanol gave a 20% yield of methyl (2-fluoro-2, 2-dinitroethyl)carbamate. In this way, the ethyl and isopropyl esters were also prepared. The preparation of 2-fluoro-2, 2-dinitroethylamine derivatives in this way avoids the hazardous[3] isolation of

2-fluoro-2,2-dinitroethylamine.

$$FC(NO_2)_2CH_2OH + NH_3 \longrightarrow FC(NO_2)_2CH_2NH_2$$

$$\xrightarrow{ROCOCl} FC(NO_2)_2CH_2NHCO_2R$$

Isopropyl (2-fluoro-2,2-dinitroethyl)carbamate was hydrolyzed in concentrated sulfuric acid to give 2-fluoro-2,2-dinitroethylammonium bisulfate, which was identified in solution by its nmr spectra (see Experimental). Dilution of the sulfuric acid solution with ether gave a white solid which was too unstable for analysis.

$$FC(NO_2)_2CH_2NHCO_2CH(CH_3)_2 \xrightarrow{H_2SO_4} FC(NO_2)_2CH_2\overset{\oplus}{N}H_3\overset{\ominus}{HSO_4}$$

EXPERIMENTAL

(2-Fluoro-2,2-dinitroethyl)methylamine. - To a stirred solution of 6.75 g (0.1 mol) of methylamine hydrochloride and 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 100 ml of water at 25° was added dropwise (5 min) a solution of 4.0 g (0.1 mol) of sodium hydroxide in 15 ml of water. After 10 min the reaction mixture was extracted with 50 ml of carbon tetrachloride and the extract was distilled to give 12.0 g (72% yield) of (2-fluoro-2,2-dinitroethyl)methylamine, a pale-yellow liquid, bp 32° (0.1 mm).

Anal. Calcd for $C_3H_6N_3O_4$: C, 21.6; H, 3.6; N, 25.2; F, 11.4. Found: C, 21.9; H, 3.7; N, 24.8; F, 11.6.

Proton nmr (CCl_4): δ 1.29 (s, NH), 2.55 (s, CH_3), and 3.83 (d, J_{HF} = 18.7 Hz, CH_2CF). Fluorine nmr: ϕ 109.8 (s, broad).

(2-Fluoro-2,2-dinitroethyl)methylamine hydrochloride, mp 120-121°, was obtained in 85% yield by reacting the amine with ethanolic hydrogen chloride. The salt precipitated upon addition of diethyl ether.

Anal. Calcd for $C_3H_7N_3FClO_4$: C, 17.7; H, 3.5; N, 20.6; F, 9.3. Found: C, 17.6; H, 3.5; N, 20.6; F, 9.4.

(2-Fluoro-2,2-dinitroethyl)dimethylamine. - The title compound, a pale-yellow liquid, bp 23-24° (0.1 mm), was obtained in 78% yield following the above procedure.

Anal. Calcd for $C_4H_8N_3FO_4$: C, 26.5; H, 4.4; N, 23.2; F, 10.4. Found: C, 26.5; H, 4.7; N, 22.8; F, 10.0.

(2-Fluoro-2,2-dinitroethyl)dimethylamine hydrochloride, mp 110-111°, was obtained in 92% yield from the amine following the above described procedure.

Anal. Calcd for $C_4H_9N_3FClO_4$: C, 22.1; H, 4.2; N, 19.3; F, 8.7. Found: C, 22.0; H, 4.4; N, 18.7; F, 8.9.

(2-Fluoro-2,2-dinitroethyl)aminoacetic Acid. --A solution of 4.0 g (0.1 mol) of sodium hydroxide in 15 ml of water was added dropwise (5 min) at 0-3° to a stirred solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol and 7.5 g of glycine (0.1 mol) in 50 ml of water. The solution turned turbid and deposited a white solid. After 30 minutes the reaction mixture was acidified with 20% hydrochloric acid. The solid was filtered, washed with water and air dried to give 13.5 g (64% yield), mp 75-76°. Recrystallization from methylene chloride gave a white crystalline solid, mp 76°.

Anal. Calcd for $C_4H_6N_3FO_6$: C, 22.8; H, 2.8; N, 19.9; F, 9.0. Found: C, 22.6; H, 2.6; N, 19.7; F, 9.0.

The infrared spectrum showed the following major peaks (μ): 2.90, 3.70, 3.93, 5.70, 5.80, 6.30, 7.62, 8.12, 11.72, and 12.50.

Proton nmr (d_6-acetone-$CDCl_3$): δ6.31 (3, NH and COOH), 3.97 (d, J_{HF}= 18.0 Hz, $-CH_2CF-$), and 3.57 (s, CH_2COO). Fluorine nmr: Φ109.7 (t, J_{HF}= 18.1).

Ethyl 2-Fluoro-2,2-dinitroethylaminoacetate. -A solution of 1.6 g (0.04 mol) of sodium hydroxide in 15 ml of water was added dropwise at 0-5° to a stirred solution of 5.6 g (0.04 mol) of glycine ethyl ester hydrochloride and 6.24 g (0.04 mol) of 2-fluoro-2,2-dinitroethanol in 75 ml of water. The resulting mixture was stirred for 20 min and then was extracted with 35 ml

of methylene chloride. The methylene chloride extract was distilled to give 9.3 g (97% yield) of ethyl 2-fluoro-2,2-dinitroethylaminoacetate, a colorless liquid, bp 95° (0.1 mm).

Anal. Calcd for $C_6H_{10}N_3FO_6$: C, 30.1; H, 4.2; N, 17.6; F, 7.9. Found: C, 29.8; H, 3.9; N, 17.5; F, 7.9.

Proton nmr (CCl_4): δ4.02 (d, d, J_{HF}= 18 Hz, J_{H-NH}= 7.5 Hz, $-CH_2CF-$), 4.17 (q, J = 7.5 Hz, $-COOCH_2-$), 3.47 (d, J= 6.8 Hz, $-CH_2CO-$), 2.24 (quin., J = 6.8 Hz, NH), and 1.27 (t, J = 7.5 Hz, CH_3). After D_2O exchange the δ4.02 quartet was reduced to a doublet; the $-CH_2O-$ doublet to a singlet, and -NH- quintet was eliminated. Fluorine nmr: φ110.2 (t, J_{HF}= 18.3 Hz).

(2-Fluoro-2,2-dinitroethyl)aminoacetaldehyde Diethyl Acetal. -To a solution of 3.1 g (0.02 mol) of 2-fluoro-2,2-dinitroethanol in 25 ml of ice water was added with stirring 2.2 g (0.017 mol) of aminoacetaldehyde diethyl acetal. The reaction mixture was stirred for 1 hr at 10-15° and then extracted with 25 ml of methylene chloride. The extract was distilled to give 4.2 g (94% yield) of a pale-yellow liquid, bp 94-95° (0.1 mm).

Anal. Calcd for $C_8H_{16}N_3FO_6$: C, 35.7; H, 5.9; N, 15.6; F, 7.1. Found: C, 35.1; H, 5.7; N, 15.1; F, 6.8.

Proton nmr (undiluted sample); δ1.21 (t, J = 7.5 Hz, CH_3), 3.6 (m, OCH_2), 1.92 (s, NH), 2.80 (d, NCH_2), 4.01 (d, J_{HF} = 17.8 Hz, $-CH_2CF$), and 4.50 (t, OCHO). Fluorine nmr: φ109.5 (t, J_{HF} = 18.0 Hz).

(2-Fluoro-2,2-dinitroethyl)aminosuccinic Acid. -To a stirred suspension of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol and 13.3 g (0.1 mol) of d, l-aspartic acid in 200 ml of water was added with stirring at 15° a solution

of 8.0 g (0.2 mol) of sodium hydroxide in 15 ml of water. The reaction mixture was stirred for 30 min and then was acidified with 20 g of concentrated hydrochloric acid. A white amorphous solid was collected, washed with water, and air dried to give 21 g (78% yield), mp 140-142°.

Anal. Calcd for $C_8H_8N_3FO_8$: C, 27.0; H, 3.0; N, 15.7; F, 7.1. Found: C, 26.8; H, 3.0; N, 15.1; F, 7.0.

Proton nmr (d_6-acetone): δ8.30 (s, NH and COOH), 4.31 (double AB quartet, J_{AB} = 15.1 Hz, $J_{AF} = J_{BF}$ = 15.0 Hz, CH_2CF), 3.83 (t, J_{HH} = 6.0 Hz, CH), and 2.82 (d, J_{HH} = 6.0 Hz, CH_2COO). Fluorine nmr: Φ109.8 (m).

2-(2-Fluoro-2,2-dinitroethylamino)ethanol. - 2-Aminoethanol, 6.1 g (0.1 mol), was added dropwise at 0-3° to a stirred solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 75 ml of water. The reaction mixture was stirred at 22° for 45 min and then was extracted with two 35 ml portions of methylene chloride. The combined extracts were concentrated and dried at 80° (0.1 mm) to give 14.5 g (74% yield), of pale yellow liquid. An analytical sample was distilled in a molecular still at 75-80° (0.005 mm).

Anal. Calcd for $C_4H_8N_3FO_5$: C, 24.4; H, 4.1; N, 21.3; F, 9.6. Found: C, 24.1; H, 4.0; N, 21.3; F, 9.5.

The differential thermal analysis exhibited a sharp exotherm at 128°, with onset of exotherm at ca. 93°.

N-(2-Fluoro-2,2-dinitroethyl)allylamine. -2-Fluoro-2,2-dinitroethanol, 6.24 g (0.04 mol) was added dropwise (10 min) at 0-10° to a stirred solution of 2.3 g (0.04 mol) of allylamine in 40 ml of water. A water-insoluble liquid separated instantaneously. After 10 min the reaction mixture was extracted with 30 ml of methylene chloride and the extract was

distilled to give 5.8 g (75% yield) of N-(2-fluoro-2,2-dinitroethyl)-allylamine, a pale-yellow liquid, bp 64-65 (0.05 mm).

Anal. Calcd for $C_5H_8N_3FO_4$: C, 30.1; H, 4.1; N, 21.8; F, 9.8. Found: C, 29.9; H, 3.9; N, 20.9; F, 9.5.

Proton nmr ($CDCl_3$): δ5.84 (m, -CH=), 5.15 (complex d, $=CH_2$), 3.92 (d, J_{HF} = 19.7 Hz, CH_2CF), 3.33 (d, allylic CH_2), and 1.77 (s, NH). Fluorine nmr: ϕ109.3 (t, J_{HF} = 20.4 Hz).

The compound was also prepared in non-aqueous solution as follows. A solution of 5.6 g (0.1 mol) of allylamine in 35 ml of methylene chloride was added dropwise (10 min) at 12-15° to a stirred solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 85 ml of methylene chloride. The reaction mixture was dried with anhydrous sodium sulfate for 2 hrs, filtered, and the filtrate was distilled to give 17.9 g (93% yield) of N-(2-fluoro-2,2-dinitroethyl)allylamine.

N,N-Bis(2-fluoro-2,2-dinitroethyl)allylamine. - A mixture of 2.5 g (0.013 mol) of N-(2-fluoro-2,2-dinitroethyl)allylamine (above) and 5.0 g of 2-fluoro-2,2-dinitroethanol was heated at 90-95° for 6 hrs. Excess alcohol was removed by distillation and the remaining viscous liquid was distilled in a molecular still at 90-95° (25-50μ) to give 2.1 g (49% yield) of N,N-bis(2-fluoro-2,2-dinitroethyl)allylamine, a pale yellow liquid.

Anal. Calcd for $C_7H_9N_5F_2O_8$: C, 25.5; H, 2.7; N, 21.3; F, 11.6. Found: C, 26.0; H, 2.1; N, 21.2; F, 11.6.

Proton nmr ($CDCl_3$): δ5.40 (m, $-CH=CH_2$), 4.11 (d, J_{HF} = 18.0 Hz, $-CH_2CF$), and 3.37 (d, J = 5.5 Hz, allylic CH_2). Fluorine nmr: ϕ108.2 (t).

N, N'-bis-(2-Fluoro-2, 2-dinitroethyl)-N, N'-bis(carbethoxymethyl)-methylenediamine. - A mixture of 7.2 g (0.03 mol) of ethyl 2-fluoro-2, 2-dinitroethylaminoacetate and 10.0 g (0.065 mol) of 2-fluoro-2, 2-dinitroethanol was heated at 115-120° for 4.5 hrs. The solution was cooled to 80° and excess of the alcohol was removed at reduced pressure. The residue crystallized on standing at 25° for several days, and was recrystallized from methanol to give 5.3 g of white solid, mp 87°.

Anal. Calcd for $C_{13}H_{20}N_6F_2O_{12}$: C, 31.8; H, 4.1; N, 17.2; F, 7.8. Found: C, 32.1; H, 4.1; N, 17.3; F, 7.8.

The infrared spectrum showed no absorption in the OH or NH region; a strong CO at 5.78 μ and NO_2 at 6.26 μ.

Proton nmr ($CDCl_3$): δ1.32 (t, J_{HH} = 7.1 Hz, CH_3), 3.44 (s, CH_2COO), 3.90 (s, NCH_2N), 4.10 (d, J_{HF} = 19.0 Hz, CH_2CF), and 4.20 (q, J_{HH} = 7.2 Hz, OCH_2). Area ratio: 3:2:1:2:2. Fluorine nmr: ϕ110.0 (t, J_{HF} = 19 Hz.).

N, N'-Bis(2-fluoro-2, 2-dinitroethyl)hydrazine. - A solution of 1.25 g (0.025 mol) of hydrazine hydrate and 7.7 g (0.05 mol) of 2-fluoro-2, 2-dinitroethanol in 220 ml of water was allowed to stand at 0° for four days. A pale yellow solid was washed with water, dried, and crystallized from chloroform to give 1.5 g (20% yield) of N, N'-bis(2-fluoro-2, 2-dinitroethyl)-hydrazine, mp 61-62°.

Anal. Calcd for $C_4H_6N_6F_2O_8$: C, 15.8; H, 2.0; N, 27.6; F, 12.5. Found: C, 16.1; H, 1.8; N, 26.8; F, 12.4.

The differential thermal analysis exhibited an endotherm at 61° and the exotherm at 141° (onset at ca. 116°).

Proton nmr (d_6-acetone): δ4.98 (m, 2 NH) and 4.19 (d, d, J_{HF} = 17.5 Hz, J_{H-NH} = 5.2 Hz, CH_2CF). Fluorine nmr: ϕ109.0 (t). When the proton spectrum was recorded at -50°, the NH signal appeared as a resolved triplet and the CH_2 signal retained its profile. The proton nmr spectrum in d_6-acetone-methylene chloride mixture exhibited a broadened doublet at δ4.10, J = 13.0 Hz, and a broad singlet at 4.21. The latter signal disappeared in D_2O exchange.

Ethyl (2-Fluoro-2,2-dinitroethyl)carbamate. - To a stirred solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 70 ml of water at 25° was added dropwise (5 min) 6.0 g of 28% ammonium hydroxide (0.1 mol of NH_3). Some yellow oil deposited. After 30 min, 5.4 g (0.05 mol) of ethyl chloroformate was added. The mixture was stirred for 10 min and a solution of 4.0 g (0.1 mol) of sodium hydroxide in 25 ml of water, another 5.4 g of ethyl chloroformate were added. After 25 min the reaction mixture was extracted with 50 ml of methylene chloride and the extract was distilled to give 15.0 g of 2-fluoro-2,2-dinitroethyl ethyl carbonate, bp 54° (0.1 mm), n_D^{25} 1.4212, lit[8], bp 53-54° (0.1 mm). Further distillation yielded 4.0 g of ethyl (2-fluoro-2,2-dinitroethyl)carbamate, a colorless liquid, bp 85°/0.1 mm.

Anal. Calcd for $C_5H_8N_3FO_6$: C, 26.7; H, 3.6; N, 18.7; F, 8.4. Found: C, 26.6; H, 3.9; N, 17.8; F, 9.0.

Proton nmr (CCl_4): δ1.23 (t, CH_3 of C_2H_5), 4.10 (q, OCH_2), 4.46 (q, J_{HF} = 15.1 Hz, CH_2CF), and 5.93 (t, NH). Fluorine nmr: ϕ109.5 (t, J_{HF} = 14.9 Hz).

Methyl (2-Fluoro-2,2-dinitroethyl)carbamate. - The title compound, a white solid, mp 40-41°, was obtained in 20% yield by reacting an ammoniacal solution of 2-fluoro-2,2-dinitroethanol with methyl chloroformate as described above.

Anal. Calcd for $C_4H_6N_3FO_6$: C, 22.8; H, 2.9; N, 19.9; F, 9.0. Found: C, 22.8; H, 3.2; N, 20.1; F, 9.1.

Isopropyl (2-Fluoro-2,2-dinitroethyl)carbamate. - The title compound, mp 47-48°, was obtained in 30% yield (together with larger quantities of 2-fluoro-2,2-dinitroethyl isopropyl carbonate) in the reaction of 2-fluoro-2,2-dinitroethanol with aqueous ammonia and isopropyl chloroformate following the above procedure.

Anal. Calcd for $C_6H_{10}N_3FO_6$: C, 30.1; H, 4.2; N, 17.6; F, 7.9. Found: C, 29.9; H, 3.9; N, 16.8; F, 7.9.

2-Fluoro-2,2-dinitroethylammonium Bisulfate. - Isopropyl (2-fluoro-2,2-dinitroethyl)carbamate (0.2 g) was added with stirring to 1.0 ml of concentrated sulfuric acid at 0-5°. Carbon dioxide was evolved. After 15 min the reaction mixture was added to 50 ml of diethyl ether and the solution was kept at -15° for 18 hrs. A white crystalline solid was filtered and washed with four 10 ml portions of diethyl ether. The solid fumed off soon after washing.

The above reaction was repeated and the sulfuric acid solution of the salt was examined by nmr. Proton nmr: δ6.60 (s, broad, A = 153, NH_3^+) and 4.00 (d, q, J_{HF} = 11.0 Hz, J_{NH-H} = 6.0 Hz, A = 102, CH_2). Fluorine nmr: Φ101.0 (t, J_{HF} = 10.4 Hz).

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SYNTHESIS OF N-FLUORONITRAMINES

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Little work has been reported on the synthesis and reactions of N-halo-N-nitroamine derivatives. N, N'-Dichloro-N,N'-dinitro-1, 2-ethylenediamine, isolated by Smart and Wright[2] in 1948, remained the sole example of this class of compounds until recently when Russian workers[3] synthesized simple N-chloro-N-nitroalkylamines by chlorinating aqueous salts of primary alkylnitramines. The synthesis of N-chloro-N-nitrocarbamates by this method was reported by Thomas[4] in 1955.

N-Bromo-N-nitroamine derivatives have not been reported. N-Chloro-N-nitroamines and N-chloro-N-nitrocarbamates are explosive compounds[2] and decompose rapidly on storage.[4]

We have synthesized N-fluoro-N-nitro-n-butylamine, the first N-fluoronitramine, by two independent, generally applicable procedures. The compound was obtained in 84% yield in the fluorination of aqueous alkali salts of n-butylnitramine under reaction conditions similar to those employed in the fluorination of aqueous nitronate salts[5] and carboxylic acid salts[6]:

$$\underline{n}\text{-}C_4H_9NNO_2^-K^+ + F_2 \longrightarrow \underline{n}\text{-}C_4H_9NFNO_2 + KF$$

The compound was characterized by elemental analysis, infrared and nmr spectra. Its fluorine nmr spectrum exhibited a triplet at ϕ -1.10. N-Fluoro-N-nitro-n-butylamine was stored at room temperature for several months

without apparent decomposition. On the other hand, in one instance a sample of the compound exploded on distillation at 60°. This method of preparation of N-fluoro-N-nitroamines is of general utility. Our procedure was used by Graff et al[7, 8] to synthesize the other two isomers of N-fluoro-N-nitrobutylamine for thermal stability studies.

N-Fluoro-N-nitro-n-butylamine was also synthesized by reacting methyl N-n-butyl-N-fluorocarbamate with 100% nitric acid:

$$\underline{n}\text{-}C_4H_9NFCOOCH_3 + HNO_3 \longrightarrow \underline{n}\text{-}C_4H_9NFNO_2 + CO_2 + CH_3ONO_2$$

Since N-alkyl-N-fluorocarbamates are readily available by the fluorination of alkylcarbamates[9], this route to N-fluoro-N-nitroamines is also of general synthetic utility.

The nitrolysis of N-n-butyl-N-fluorocarbamate most likely proceeds by the electrophilic displacement of carbomethoxycarbonium ion by nitronium ion:

$$C_4H_9NFCOOCH_3 + NO_2^+ \longrightarrow C_4H_9NFNO_2 + \left[{}^+COOCH_3\right]$$

This mechanism is analogous to that proposed for the fluorinolysis of N-alkyl-N-fluorocarbamates to the corresponding N, N-difluoroalkylamines[9]. The nitrolysis of N, N-dialkylformamides was reported by Robson.[10]

Experimental Section

Fluorinations were conducted in a three-necked flask following the previously described technique.[5, 6] Adequate safety shielding should be used when handling N-fluoro-N-nitro-n-butylamine.

N-Fluoro-N-nitro-n-butylamine. - (1) By direct fluorination. Aqueous potassium salt of n-butylnitramine, prepared by dissolving 11.8 g (0.1 mol) of n-butylnitramine in a solution of 0.1 mol of potassium hydroxide in 250 ml

of water, was fluorinated with 0.1 mol fluorine over a period of 45 min. A pale-yellow liquid separated from the solution as the fluorination progressed. The reaction mixture was extracted with 70 ml of methylene chloride. The extract was washed with 75 ml of cold saturated aqueous solution of sodium bicarbonate, and with 75 ml of water. The methylene chloride solution was dried with anhydrous sodium sulfate and distilled to give 11.5 g (86% yield) of N-fluoro-N-nitro-n-butylamine, bp 40°/25 mm.

Anal. Calcd for $C_4H_9N_2FO_2$: C, 35.3; H, 6.7; N, 20.6; F, 14.0. Found: C, 35.0; H, 6.3; N, 21.2; F, 14.3.

The infrared spectrum consisted of the following peaks (μ): 3.39(m), 3.50(m), 6.18(s), 6.35(sh), 6.84(w), 7.01(w), 7.25(w), 7.55(sh), 7.76(s), 7.93(sh), 8.14(w), 8.96(w), 9.40(w), 9.61(w), 10.05(w), 11.35(m), and 12.10(m).

Proton nmr (CCl_4): 59 Hz from TMS(m, CH_3), 97 Hz from TMS (m, two internal CH_2), and δ6.07 (d, t, J_{HF}=35 Hz, J_{HH}=11 Hz, α-CH_2). Fluorine nmr: φ -1.10 (t, J_{HF}=33.5 Hz).

(2) By Nitration. - To 25 ml of 100% nitric acid at -5° was added dropwise with stirring 4.0 g (0.027 mol) of methyl N-n-butyl-N-fluorocarbamate over a period of 15 min. Carbon dioxide was evolved. The mixture was stirred for 20 min and then poured on 100 g of crushed ice. The product was extracted with two 20 ml portions of methylene chloride, dried over sodium sulfate and distilled to give 3.1 g (84% yield) of N-fluoro-N-nitro-n-butylamine, bp 40°/25 mm.

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SYNTHESIS OF TRIS (CARBOALKOXYAMINO) METHANE AND N-CARBETHOXYIMINOCARBOXYLIC ACID ESTERS [1]

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Only few tris (amino) methane derivatives of the general structure $HC(NHR)_3$ are known. Tris (formamido) methane (N, N', N''-methylidynetrisformamide) and tris (acetamido)methane were reported by Pinner[2] in 1883. Several higher homologues of this series were recently synthesized by Bredereck et al[3] by heating ethyl orthoformate with amides in the presence of a catalytic amount of sulfuric acid.

We have now synthesized tris (carboalkoxyamino)methanes by heating ethyl orthoformate with alkyl carbamates and using aniline sulfate as the catalyst:

$$HC(OC_2H_5)_3 + 3\ NH_2COOR \xrightarrow[\Delta]{\text{Aniline sulfate}} HC(NHCOOR)_3 + 3\ C_2H_5OH$$

$R=CH_3,\ C_2H_5$

The compounds, obtained in 45-55% yields, were characterized by elemental analysis and nmr spectra. For comparison, the proton nmr spectrum of tris (acetamido)methane was also obtained (see Experimental) and was found to be very similar to that of tris (carbethoxyamino)methane.

Reactions of higher ortho esters with urethanewere also investigated under similar reaction conditions, and were found to give different products. Thus, urethane reacted with triethyl orthoacetate or triethyl orthopropionate to give

ethyl N-carbethoxy-acetimidate and ethyl N-carbethoxypropioimidate, respectively:

$$RC(OC_2H_5)_3 + NH_2COOC_2H_5 \xrightarrow[\Delta]{\text{Aniline sulfate}} \underset{\displaystyle OC_2H_5}{\overset{\displaystyle |}{RC{=}NCOOC_2H_5}}$$

$R=CH_3,\ C_2H_5$

N-Carbethoxyiminocarboxylic acid esters are colorless liquids, sparingly soluble in water, and stable at room temperature.

Experimental Section

Tris (carbethoxyamino)methane. - A mixture containing 40 g (0.27 mol) of ethyl orthoformate, 74 g (0.81 mol) of ethyl carbamate, and 0.7 g of aniline sulfate was heated in a distillation apparatus at 115-125° for 2.5 hrs. During this time 32 ml of ethanol distilled over. The temperature was then increased to 155° for 1.5 hrs, and additional 13 ml of ethanol was removed. The reaction mixture was cooled and the crude material was recrystallized from methylene chloride to give 41 g (55% yield) of tris (carbethoxyamino)methane, a white crystalline solid, mp 210-211°.

Anal. Calcd for $C_{10}H_{19}N_3O_6$: C, 43.31; H, 6.91; N, 15.16. Found: C, 43.11; H, 6.82; N, 15.03.

Proton nmr (DMSO-d_6): δ 7.45 (d, J=7.0 Hz, β, NH), 6.24 (q, J=7.0 Hz, 1, CH), 4.03 (q, J=7.1 Hz, 6, CH_2), and 1.20 (t, J=7.0 Hz, 9, CH_3).

Proton nmr spectrum (DMSO) of tris (acetamido)methane: δ 7.42 (d, J=7.2 Hz, 3, NH), 6.12 (q, J=7.0 Hz, 1, CH), and 3.62 (s, 9, CH_3).

Tris (carbomethoxyamino)methane. - The title compound was synthesized from ethyl orthoformate and methyl carbamate in 45% yield following the above

procedure. The crude solid was crystallized from methanol, mp 177-178°.

Anal. Calcd for $C_7H_{13}N_3O_6$: C, 35.74; H, 5.57; N, 17.87. Found: C, 36.11; H, 5.62; N, 17.81.

In a separate experiment, a mixture of ethyl orthoformate and methyl carbamate was heated at 145° for 2 hrs in the absence of aniline sulfate. No ethanol was liberated and only the starting materials were isolated from the reaction mixture at the end of the experiment.

Ethyl N-Carbethoxyacetimidate. - A mixture containing 32.5 g (0.2 mol) of ethyl orthoacetate, 60 g (0.4 mol) of ethyl carbamate, and 0.7 g of aniline sulfate was heated in a distillation apparatus at 110-120° for 1.5 hr. During this time 20 ml of ethanol was distilled. The reaction mixture was cooled to 5° and the excess of ethyl carbamate was removed by filtration. The fitrate was dissolved in 150 ml of carbon tetrachloride and the solution was washed with four 100 ml portions of water in order to remove the remaining ethyl carbamate. The carbon tetrachloride solution was distilled to give 21 g (66% yield) of a colorless liquid, bp 90-91/25 mm.

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.51; H, 8.01; N, 8.97.

Ethyl N-Carbethoxypropioimidate. - The title compound, bp 38-39°/0.1mm, was prepared in 58% yield from ethyl orthopropionate and ethyl carbamate following the above procedure.

Anal. Calcd for $C_8H_{15}NO_3$: C, 55.52; H, 8.73; N, 8.02. Found: C, 55.34; H, 8.62; N, 8.17.

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References

1. This work was supported by the Office of Naval Research.
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3. H. Bredereck, F. Effenberger, and H. J. Treiber, ibid., 96, 1505 (1963).

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Alkylation reactions of difluoramine and direct fluorination reactions are reviewed. The following phases of earlier work were completed and the work was assembled in the form of manuscripts:

Mannich Reactions of 2-Fluoro-2,2-dinitroethanol;

Synthesis of N-Fluoronitramines;

Synthesis of Tris(carboalkoxyamino)methane;

N-Carbethoxyiminocarboxylic Acid Esters.

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